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NEUROLOGICAL AND INTELLECTUAL STATUS OF PREMATURES AT THREE TO FIVE YEARS OF AGE

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AS MORE attempts are made to follow the course of development of prematurely born children, a clearer understanding is obtained of their position relative to their full-term contemporaries. In relation to neurological and intellectual status, it is possible to find in the recent literature data indicating little or no difference between children born prematurely and those born at term as well as data at variance with this conclusion. The weight of the evidence, however, seems to indicate clear differences.[1-4] The findings reported in this paper suggest that prematurely born children are more often handicapped than those born at term, at least through the fifth year of life.

SOURCE OF MATERIAL AND PROCEDURES

In 1952, a long-term study of prematurely born infants was undertaken by the Maternal and Child Health Division of the Johns Hopkins University, School of Hygiene and Public Health. An early part of the Study was concerned with evaluating current standards for hospital care of prematures[5] and dealt with the nearly 4,700 prematures (live born, weighing less than 2,501 grams, 5½ pounds, at birth) born in Maryland in 1952 and with the 46 Maryland hospitals concerned with their care. Various data relating to the prenatal, delivery, and neonatal history of these children were obtained at that time. About 500 of these prematures who were born in Baltimore were selected for long-term follow-up and they were matched at birth with an equal number of full-term babies. Further details concerning the selection and matching are reported elsewhere.[6]

One purpose in following these children for a number of years is to ascertain the extent to which surviving prematurely born infants differ from full-term ones in their subsequent development. The procedure for gathering information related to this question

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has consisted of periodic examinations of the children and interviews with the mothers, at which times specific data were obtained as uniformly as possible and, in so far as could be, with the prematurity status of the child unknown to the person conducting the examination or the interview. The first such round of examinations and interviews took place when the children were about 40 weeks of age; the second when they were from 3 to 5 years of age; and a third is in progress during their seventh and eighth years of age.

The present report summarizes the findings on neurologic and intellectual status as determined on the second round of examinations, and relates these findings to those of the 40 week examinations which were previously reported.[6]

At the 40 week examination 992 infants were seen. This was 85 per cent of those selected for the examination. Three and one half per cent of the interviews were refused and 11.5 per cent of the children could not be located. For the second round of examinations a follow-up was attempted on only the 992 studied at 40 weeks. Nine hundred, or 91 per cent, of these were seen. Three and six tenths per cent refused; 0.7 per cent had died; 4.4 per cent had moved too far away to be followed; and 0.5 per cent could not be located.

The 9 per cent loss between the two examinations altered only slightly the comparability of the premature and control groups. At 40 weeks an excess of non-whites with birth weights below 2,001 grams was noted. This excess has increased slightly. Within each racial group, however, no significant differences between birth weight groups have been found in various indices of socioeconomic status. The indices examined were economic tenth of residence (based on median rental of census tract),[6] home ownership, proportion unemployed, father's occupational group, total family income, mother's education, and others. Therefore, if race is taken into account, it seems probable that the birth weight comparisons and, consequently, the premature-control comparisons which follow are valid.

During the second round of examinations the children ranged in ages from 29 to 62 months, with 92 per cent being seen when they were between 3 and 4.5 years of age. This examination consisted of two parts: a home interview and an office examination. The home interview was designed to ascertain various characteristics of the child's family and environment together with certain behavior items as reported by the person interviewed, usually the mother. Also the home interview provided opportunity to describe and make an appointment for the second part of this round of observations, a developmental examination conducted at the Study offices.

The office examination made use of the Gesell Developmental scales from the 24 month to the 60 month level as well as the Revised Stanford-Binet Form L for the corresponding age levels. When an alternate Binet item was the same as one included in the Gesell scale the alternate was the one selected for use. This procedure allowed scoring in both Gesell and Binet terms. A physical examination was also obtained in about 65 per cent of the cases.

The first third of the developmental examinations, 297 cases, was done by a pediatrician (H. K.) especially trained in this field. The last two thirds were done by a psychologist (L. F.) specializing in the evaluation of the developmental level of young children. During the first third of these visits the physical examination was done along with the rest of the developmental examination by the same person. Of the remainder about a half were given physical examinations and, although done at the same visit, the physical examinations were not performed by the one carrying out the psychometric evaluation, but were divided among the pediatricians on our staff.

The principles of classification of neurological and intellectual status were essentially the same for the two examinations, although tests on which a given classification was based were made appropriate to the age group concerned. Concerning definitions of neurological status as classified at the 40 week examinations, the description given in the earlier paper[6] is repeated here. The neurological status was an estimate of the integrity of the nervous system as this was manifested by the absence or presence of impairment in neuromotor functioning and deviations in muscle tonus and control. It was expressed in terminology appropriate to the field of infant neurology that indicated the extent of departure from normal and comprised five categories. Those infants who were called "normal" were without signs of neurological damage, while those in an "indeterminate" category had such minor deviations from normal patterning that for summary purposes they were added to the normal group. Those infants who had "minimal damage" were a group with definite and distinctive deviations in neurological patterning in which clinical experience with the examination technique indicated that there would be complete compensation and no detection of abnormal neurological signs later by the standard neurological examination. Another group called "possible cerebral palsy" were infants who had signs and symptoms that would warrant a diagnosis of cerebral palsy had they been observed in an older child. Clinical experience indicated, however, that, although most infants with this degree of abnormality at 40 weeks of age eventually would compensate completely and have no neurological residua, cerebral palsy could not be definitively ruled out. The final group with "overt abnormality" had gross deviations from normal neurological patterning and were expected to continue to present abnormal neurological signs.

The differences between the 40 week and the 3 to 5 year classifications are seen in Tables I*A* and I*B*. The classes "minimal damage" and "possible cerebral palsy" are dropped at 3 to 5 years and the terms "questionable signs of minimal damage" and "signs of minimal damage" describe two degrees of abnormality falling between "normal" and "overt abnormality." "Minimal damage" when used by L. F. includes minor deviations from normal performance during psychological testing thought to be associated with congenital defect, acquired defect from any source, or retarded physical

TABLE IA. NEUROLOGICAL STATUS BY BIRTH WEIGHT AT 40 WEEKS

WEIGHT GROUP (GRAMS)	NO. (1)	PERCENTAGE IN EACH DIAGNOSTIC CATEGORY: NORMAL PLUS INDETERMINATE (2)	MINIMAL DAMAGE (3)	POSSIBLE CEREBRAL PALSY (4)	OVERT NEUROLOGICAL DEFECT (5)	TOTAL (6)
1,500 or less	57	50.9	22.8	14.0	12.3	100.0
1,501-2,000	84	73.8	14.3	9.5	2.4	100.0
2,001-2,500	359	76.9	17.3	4.5	1.4	100.1
Subtotal for premature infants, adjusted for weight distribution*		75.5	16.3	6.1	2.1	100.0
2,501 or more (controls)	492	88.4	10.0	1.0	0.6	100.0
Total	992					

*Adjusted to distribution with 5 per cent at 1,500 grams or less and 95 per cent at 1,501 to 2,500 grams.

TABLE IB. NEUROLOGICAL STATUS BY BIRTH WEIGHT AT 3 TO 5 YEARS

WEIGHT GROUP (GRAMS)	NO. (1)	PERCENTAGE IN EACH DIAGNOSTIC CATEGORY: NORMAL (2)	QUESTIONABLE SIGNS OF MINIMAL DAMAGE (3)	SIGNS OF MINIMAL DAMAGE (4)	OVERT ABNORMALITY (5)	UNKNOWN (6)	TOTAL (7)
1,500 or less	54	51.9	24.1	7.4	13.0	3.7	100.1
1,501-2,000	76	72.4	18.4	5.3	0	3.9	100.1
2,001-2,500	330	81.8	11.5	1.5	1.2	3.9	99.9
Subtotal for premature infants, adjusted for weight distribution*		78.6	13.4	2.5	1.6	3.9	100.0
2,501 or more (controls)	440	87.3	7.5	1.6	0.7	3.0	100.1
Total	900						

*Adjusted to distribution with 5 per cent at 1,500 grams or less and 95 per cent at 1,501 to 2,500 grams.

development, excluding cases of mental retardation without evident neurological injury. H. K., who examined the first third of the group, did not include among those with "minimal damage" any children who had retarded development without any neurological abnormalities. At the examination of children of 3 to 5 years it was found necessary to add the "unknown" category.

The classification of intellectual status is not simply a direct use of numerical scores as obtained from the testing, but reflects some judgment as to the validity of the numerical results. The relatively high percentage of children whose functioning could not be rated at 3 to 5 years contains children who either failed to perform in one or the other area of testing, or whose reaction to the situation was such that only the roughest samples of intellectual behavior or no response to test materials could be obtained. In such cases clinical judgment of the representativeness of sample behavior obtained was used, and the children were assigned to a definite functioning group or the "unknown" group according to this judgment. The classification is otherwise the usual one.

FINDINGS

If we turn first to the birth weight comparisons of neurological status at

3 to 5 years, the same significant* trend favoring the full-term child is found at 3 to 5 years (Tables I*A* and I*B*) as was found at 40 weeks. Because essentially no racial or examiner differences were found in the neurological status, Tables I*A* and I*B* present the data for white and non-white children and for both examiners combined.† Certain shifts in classification occurred, but these shifts do not markedly alter the birth weight comparison. There is a suggestion in these data of relative improvement for children of birth weights from 1,501 to 2,500 grams. By combining the normal group with the indeterminate group for the 40 week examination, it is found that there is little change in the proportion which could be described as "normal" and the premature-full-term comparison is much the same.

The above discussion pertains to *net* change. Table II summarizes the correlations behind Table I and shows the compensating shifts which occurred among the 900 cases seen at both the 40 week and the 3 to 5 year examination. To simplify the analysis the "indeterminate" category was again combined with the "normal" for the 40 week results, and the two classes considered abnormal but not called "overt abnormality" were grouped together for both examinations.

Looking first at the cases classified as "normal" or "indeterminate" at 40 weeks, we see that the proportion considered "normal" at 3 to 5 years increases with increased birth weight (column 7), the trend being statistically significant. This is true also for those classified at 40 weeks as "abnormal," but not called "overt abnormality," although the numbers are small. No helpful evidence on this point is found in the group considered to have an "overt abnormality" at 40 weeks, because so few were placed in this category. Nevertheless, it does appear that the smaller the baby at birth, the less likely is he to maintain the status of "normal" or to improve if not "normal" between 40 weeks of age and 3 to 5 years.

Next, examination of the clinical assessment of intellectual status shows that the favorable position of the full-term children is again maintained during the interval from the 40 week to the 3 to 5 year observation (Table III). A description of the shifting of classification that took place between the two ages is more complicated in the case of intellectual status because there are found to be racial and examiner differences in the shift.

The shift occurring among the white group will be described first since the examiner differences found here, although in some respects similar to those found for the non-whites which are shown below, were such that they did not affect interpretation of the tables presented in this paper.* Each birth weight subdivision showed a marked decrease in the proportion judged average, with complementing increases occurring both above and below the average. Although this was true for each weight group, the exact extent of the shifts was not uniform, so the net effect has been to make the

*The criterion for statistical significance in this paper is P less than 0.05, as determined by a chi-square test. Degrees of freedom may not uniformly be deduced from the tables since, in obtaining chi square, pooling was used in some instances when expected numbers were small.

†Data by examiner are available on request.

*Data by examiner are available on request.

TABLE II. NEUROLOGICAL STATUS, 40 WEEK VERSUS 3 TO 5 YEAR CORRELATION BY BIRTH WEIGHT

40 WEEK	3-5 YEAR						3-5 YEAR PERCENTAGE DISTRIBUTION OF 40 WEEK CLASSIFICATION				
					TOTAL						
	NORMAL (1)	ABNORMAL, NOT OVERT (2)	OVERT (3)	UNKNOWN (4)	NO. (5)	% (6)	NORMAL (7)	ABNORMAL, NOT OVERT (8)	OVERT (9)	UNKNOWN (10)	TOTAL (11)
Under 1,501 Grams.—											
Normal	17	10	1	—	28	51.9	60.7	35.7	3.6	—	100.0
Abnormal, not overt	10	5	2	2	19	35.2	52.6	26.3	10.5	10.5	99.9
Overt	1	2	4	—	7	13.0	14.3	28.6	57.1	—	100.0
Total No.	28	17	7	2	54	100.1					
Per cent	51.9	31.5	13.0	3.7	100.1						
1,501-2,000 Grams.—											
Normal	44	9	—	3	56	73.7	78.6	16.1	—	5.4	100.1
Abnormal, not overt	9	9	—	—	18	23.7	50.0	50.0	—	—	100.0
Overt	2	—	—	—	2	2.6	100.0	—	—	—	100.0
Total No.	55	18	—	3	76	100.0					
Per cent	72.4	23.7	—	3.9	100.0						
2,001-2,500 Grams.—											
Normal	217	25	—	9	251	76.1	86.5	10.0	—	3.6	100.1
Abnormal, not overt	53	16	2	4	75	22.7	70.7	21.3	2.7	5.3	100.0
Overt	—	2	2	—	4	1.2	—	50.0	50.0	—	100.0
Total No.	270	43	4	13	330	100.0					
Per cent	81.8	13.0	1.2	3.9	99.9						
Under 2,501 Grams.—											
Normal	278	44	1	12	335	72.8	83.0	13.1	0.3	3.6	100.0
Abnormal, not overt	72	30	4	6	112	24.3	64.3	26.8	3.6	5.4	100.1
Overt	3	4	6	—	13	2.8	23.1	30.8	46.2	—	100.1
Total No.	353	78	11	18	460	99.9					
Per cent	76.7	17.0	2.4	3.9	100.0						
Over 2,501 Grams.—											
Normal	344	31	2	9	386	87.7	89.1	8.0	0.5	2.3	99.9
Abnormal, not overt	38	9	1	3	51	11.6	74.5	17.6	2.0	5.9	100.0
Overt	2	—	—	1	3	0.7	66.7	—	—	33.3	100.0
Total No.	384	40	3	13	440	100.0					
Per cent	87.3	9.1	0.7	3.0	100.1						

relative position of the prematures less favorable. For example, at 40 weeks the premature group as a whole was estimated to have 97 per cent of its members in the low-average or above categories and the full-term children had a corresponding percentage of 98. At 3 to 5 years the proportion of prematures so classified had dropped to 84 per cent, but the full-term children only to 94 per cent.

Among non-whites the marked decline in the proportion classified as average is present as it was among white children. This was true, furthermore, for each examiner. In general, however, when examiner H. K. found a shift in a child's classification it was toward a higher class more frequently than was the case with examiner L. F., with the consequence that the net shift among the non-white children examined by H. K. was to raise the proportion classified above, as well as the proportion classified below, average in a fashion similar to the shift found among the white children. The non-white children classified by L. F., on the other hand, showed a marked reduction by 3 to 5 years in the proportion classified as above average as well as in the proportion classified as average, with the complementing increases occurring entirely below the average group.

The net effect of the over-all findings by H. K. and L. F. has been to make the relative position of the prematures less favorable among the non-white group, similarly to the effect seen above for the white. For the non-white premature infants the proportion classified as low-average or above was 93 per cent at 40 weeks and for the full-term it was 97 per cent, a difference of 4 per cent. At 3 to 5 years these proportions were 68 per cent and 79 per cent, a difference of 11.

Table IV presents for Intellectual Status, specific for race and, in the non-white groups, for examiner, correlation tables similar to those of Table II for Neurological Status. Prematures are not subdivided by birth weight in this table because within the premature group there appeared to be no trend by birth weight in the correlation between the two examinations. Again examiner difference is noted among the non-white children. It is pertinent to note in this connection that the age of the children examined by L. F. was on the average 9 months older than of those examined by H. K. It is possible that environmental factors among the non-whites, which one may reasonably presume are less advantageous than among the whites, are contributing significantly to the examiner differences since these factors have had more time to act on cases seen by L. F. It does not seem likely, however, that this can explain all of the examiner differences which were found. Table IV shows the prematures to have a less favorable prognosis for improvement or for maintaining an average or above-average level of intellectual status just as was true for neurological status. Thus, 83 per cent of the white prematures who were classified as average or low-average at 40 weeks were classified similarly or better at 3 to 5 years, as compared with 93 per cent of full-term children (columns 8 and 9, line 2 of each weight group, Table IV, A). Similar results are found in other 40 week categories and among the non-white children.

TABLE III. INTELLECTUAL STATUS AT 40 WEEKS AND 3 TO 5 YEARS, BY BIRTH WEIGHT, RACE, AND EXAMINER

WEIGHT GROUP (GRAMS)	NO. (1)	PERCENTAGE IN EACH DIAGNOSTIC CATEGORY								
		SUPERIOR (2)	HIGH AVG. (3)	AVERAGE (4)	LOW AVERAGE (5)	DULL NORMAL (6)	BORDER-LINE DEFEC-TIVE (7)	DEFEC-TIVE (8)	DEFECT, TYPE UN-CLASSI-FIED (9)	TOTAL (10)
				A. Total White						
At 40 Weeks of Age.—										
1,500 or less	18	—	16.7	66.7	5.6	5.6	—	—	5.6	100.2
1,501-2,000	29	—	3.4	75.9	13.8	3.4	—	—	3.4	99.9
2,001-2,500	166	2.4	19.9	70.5	4.8	1.8	—	0.6	—	100.0
Subtotal for premature infants, adjusted for weight distribution		2.0	17.4	71.1	6.2	2.3	—	0.5	0.8	100.3
2,501 or more (controls)	224	6.2	15.2	69.6	6.7	0.9	0.9	0.4	—	99.9
Total	437									
At 3 to 5 Years of Age.—										
1,500 or less	17	5.9	11.8	47.1*	17.6	—	11.8	—	5.9†	100.1
1,501-2,000	24	16.7	8.3	33.3	20.8	12.5	—	—	8.3	99.9
2,001-2,500	147	9.5	21.8	46.3	7.5	7.5	2.0	2.0	3.4	100.0
Subtotal for premature infants, adjusted for weight distribution		10.3	19.5	44.5	9.8	7.8	2.3	1.7	4.2	100.1
2,501 or more (controls)	197	11.2	29.9	44.7	8.6	2.0	0.5	0.5	2.5	99.9
Total	385									
				B. Total Non-white						
At 40 Weeks of Age.—										
1,500 or less	39	—	—	53.8	17.9	7.7	5.1	10.3	5.1	99.9
1,501-2,000	55	—	18.2	63.6	12.7	1.8	1.8	1.8	—	99.9
2,001-2,500	193	2.1	10.4	69.9	11.9	3.1	0.5	2.1	—	100.0
Subtotal for premature infants, adjusted for weight distribution		1.5	11.5	67.8	12.4	3.0	1.0	2.4	0.3	99.9
2,501 or more (controls)	268	5.2	15.7	66.8	9.3	1.1	—	1.5	0.4	100.0
Total	555									
At 3 to 5 Years.—										
1,500 or less	37	—	—	27.0*	21.6	24.3	5.4	18.9	2.7‡	99.9
1,501-2,000	52	—	7.7	40.4	15.4	23.1	9.6	1.9	1.9	100.0
2,001-2,500	183	1.6	4.9	41.0	22.4	19.1	6.6	2.2	2.2	100.0
Subtotal for premature infants, adjusted for weight distribution		1.2	5.2	40.2	20.9	20.2	7.1	2.9	2.1	99.8
2,501 or more (controls)	243	2.1	10.7	43.2	22.6	14.8	3.3	1.2	2.1	100.0
Total	515									

C. Non-white Examined by H. K. at 40 Weeks and at 3 to 5 Years of Age										
At 40 Weeks of Age.—										
1,500 or less	13	—	—	38.5	7.7	7.7	7.7	23.1	15.4	100.1
1,501-2,000	16	—	6.2	68.8	18.8	—	—	6.2	—	100.0
2,001-2,500	51	3.9	5.9	51.0	23.5	9.8	2.0	3.9	—	100.0
Subtotal for premature infants, adjusted for weight distribution		2.8	5.7	54.4	21.7	7.5	1.8	5.4	0.8	100.1
2,501 or more (controls)	87	3.4	8.0	69.0	11.5	2.3	—	4.6	1.1	99.9
Total	167									
At 3 to 5 Years of Age.—										
1,500 or less	13	—	—	15.4§	30.8	15.4	—	30.8	7.7‡	100.1
1,501-2,000	16	—	18.8	43.8	18.8	18.8	—	—	—	100.2
2,001-2,500	51	3.9	9.8	43.1	21.6	9.8	3.9	3.9	3.9	99.9
Subtotal for premature infants, adjusted for weight distribution		2.8	11.3	41.9	21.4	12.1	2.8	4.4	3.2	99.9
2,501 or more (controls)	87	4.6	11.5	51.7	18.4	8.0	—	3.4	2.3	99.9
Total	167									
D. Non-white Examined by H. K. at 40 Weeks and by L. F. at 3 to 5 Years of Age										
At 40 Weeks of Age.—										
1,500 or less	24	—	—	66.7	25.0	4.2	4.2	—	—	100.1
1,501-2,000	36	—	25.0	58.3	11.1	2.8	2.8	—	—	100.0
2,001-2,500	131	1.5	12.2	77.1	7.6	0.8	—	0.8	—	100.0
Subtotal for premature infants, adjusted for weight distribution		1.1	14.2	72.8	9.2	1.3	0.7	0.6	—	99.9
2,501 or more (controls)	156	7.1	17.9	64.7	9.6	0.6	—	—	—	99.9
Total	347									
At 3 to 5 Years of Age.—										
1,500 or less	24	—	—	33.3‖	16.7	29.2	8.3	12.5	—‡	100.0
1,501-2,000	36	—	2.8	38.9	13.9	25.0	13.9	2.8	2.8	100.1
2,001-2,500	132	0.8	3.0	40.2	22.7	22.7	7.6	1.5	1.5	100.0
Subtotal for premature infants, adjusted for weight distribution		0.6	2.8	39.6	20.6	23.5	8.9	2.3	1.7	100.0
2,501 or more (controls)	156	0.6	10.3	39.1	25.0	17.9	5.1	—	1.9	99.9
Total	348									

*Approximately 10 per cent of cases seen at 3 to 5 years were classified Indeterminate, but in Normal Range, i.e., Dull Normal or better. These have been included in column 4, Average.

†Cases classified at 3 to 5 years as Indeterminate, Unknown.

‡See Table 3, *A*.

§Approximately 4 per cent of cases seen at 3 to 5 years were classified Indeterminate, but in Normal Range, i.e., Dull Normal or better. These have been included in column 4, Average.

‖Approximately 13 per cent of cases seen at 3 to 5 years were classified Indeterminate, but in Normal Range, i.e., Dull Normal or better. These have been included in column 4, Average.

TABLE IV. INTELLECTUAL STATUS, 40 WEEK VERSUS 3 TO 5 YEAR CORRELATION BY BIRTH WEIGHT, RACE, AND EXAMINER

40 WEEKS	3-5 YEARS: SUPERIOR HIGH AVERAGE (1)	AVERAGE LOW AVERAGE (2)	DULL NORMAL BORDERLINE (3)	DEFECTIVE (4)	INDETERMINATE (5)	TOTAL NO. (6)	TOTAL % (7)	3-5 YEAR PERCENTAGE OF 40 WEEK CLASS: SUPERIOR HIGH AVERAGE (8)	AVERAGE LOW AVERAGE (9)	DULL NORMAL BORDERLINE (10)	DEFECTIVE (11)	INDETERMINATE (12)	TOTAL (13)
						A. Total White							
Under 2,501 Grams.—													
Superior and high average	18	17	1	—	—	36	19.1	50.0	47.2	2.8	—	—	100.0
Average and low average	36	84	15	3	7	145	77.1	24.8	57.9	10.3	2.1	4.8	99.9
Dull normal and borderline	1	1	2	—	—	4	2.1	25.0	25.0	50.0	—	—	100.0
Defective	—	—	1	—	—	1	0.5	—	—	100.0	—	—	100.0
Indeterminate defect	—	1	—	—	1	2	1.1	—	50.0	—	—	50.0	100.0
Total													
No.	55	103	19	3	8	188	99.9						
%	29.3	54.8	10.1	1.6	4.3	100.1							
2,501 Grams or More.—													
Superior and high average	25	19	—	—	—	44	22.3	56.8	43.2	—	—	—	100.0
Average and low average	56	85	4	1	5	151	76.6	37.1	56.3	2.6	0.7	3.3	100.0
Dull normal and borderline	—	1	—	—	—	1	0.5	—	100.0	—	—	—	100.0
Defective	—	—	1	—	—	1	0.5	—	—	100.0	—	—	100.0
Indeterminate defect	—	—	—	—	—	—	—	—	—	—	—	—	—
Total													
No.	81	105	5	1	5	197	99.9						
%	41.1	53.3	2.5	0.5	2.5	99.9							
						B. Non-white Examined by H. K. at 40 Weeks and 3 to 5 Years							
Under 2,501 Grams.—													
Superior and high average	2	4	—	—	—	6	7.5	33.3	66.7	—	—	—	100.0
Average and low average	8	42	5	1	2	58	72.5	13.8	72.4	8.6	1.7	3.4	99.9
Dull normal and borderline	—	3	4	1	—	8	10.0	—	37.5	50.0	12.5	—	100.0
Defective	—	—	3	3	—	6	7.5	—	—	50.0	50.0	—	100.0
Indeterminate defect	—	—	—	1	1	2	2.5	—	—	—	50.0	50.0	100.0
Total													
No.	10	49	12	6	3	80	100.0						
%	12.5	61.2	15.0	7.5	3.8	100.0							

2,501 Grams or More.—													
Superior and high average	3	7	—	—	—	10	11.5	30.0	70.0	—	—	—	100.0
Average and low average	11	51	6	—	2	70	80.5	15.7	72.9	8.6	—	2.9	100.1
Dull normal and borderline	—	2	—	—	—	2	2.3	—	100.0	—	—	—	100.0
Defective	—	1	—	3	—	4	4.6	—	25.0	—	75.0	—	100.0
Indeterminate defect	—	—	1	—	—	1	1.1	—	—	100.0	—	—	100.0
Total													
No.	14	61	7	3	2	87	100.0						
%	16.1	70.1	8.0	3.4	2.3	99.9							
C. Non-white Examined by H. K. at 40 Weeks and by L. F. at 3 to 5 Years													
Under 2,501 Grams.—													
Superior and high average	1	19	5	1	1	27	14.1	3.7	70.4	18.5	3.7	3.7	100.0
Average and low average	5	94	53	4	3	159	82.8	3.1	59.1	33.3	2.5	1.9	99.9
Dull normal and borderline	—	2	3	—	—	5	2.6	—	40.0	60.0	—	—	100.0
Defective	—	—	—	1	—	1	0.5	—	—	—	100	—	100.0
Indeterminate defect	—	—	—	—	—	—	—	—	—	—	—	—	—
Total													
No.	6	115	61	6	4	192	100.0						
%	3.1	59.9	31.8	3.1	2.1	100.0							
2,501 Grams or More.—													
Superior and high average	6	27	5	—	1	39	25.0	15.4	69.2	12.8	—	2.6	100.0
Average and low average	11	73	30	—	2	116	74.4	9.5	62.9	25.9	—	1.7	100.0
Dull normal and borderline	—	—	1	—	—	1	0.6	—	—	100.0	—	—	100.0
Defective	—	—	—	—	—	—	—	—	—	—	—	—	—
Indeterminate defect	—	—	—	—	—	—	—	—	—	—	—	—	—
Total													
No.	17	100	36	—	3	156	100.0						
%	10.9	64.1	23.1	—	1.9	100.0							

SUMMARY

The present report compares the neurological and intellectual status of a group of 460 prematurely born children examined at 3 to 5 years of age with that of a matched group of 440 full-term children serving as controls. The findings at this examination are related to similar data pertaining to the same children obtained when they were 40 weeks of age. At both examinations the prematurely born group was found to rate somewhat lower in intellectual status and to have a smaller proportion classed as neurologically normal than the full-term children. When the prematures were subdivided by birth weight the trend favoring those with larger birth weights was maintained. For example, those in the group with birth weights from 2,001 to 2,500 grams were only slightly different from the controls; those whose birth weights were under 1,501 grams were more seriously handicapped. Consequently, a statement about "prematures" is more useful when details regarding degree of prematurity are available. Also, it was found in comparing the 40 week and the 3 to 5 year results that a child's prognosis for improvement in classification or for maintaining an average or better rating increased with an increase in birth weight. The answer as to whether or not this finding is peculiar to this age interval or to the aspects of development discussed in this paper must await further study. Finally, while the prematurely born group performs less well than the full-term group on the two indices here studied, it should be emphasized that the great majority of those born prematurely fall within the normal range and their distribution of intelligence ratings closely approximates that found for those born at term although somewhat on the lower side.

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A STUDY OF CAUSES OF NEONATAL DEATHS

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IN MANY studies on neonatal mortality, obstetric factors have been found to play a significant role.[1-6] This might be taken to imply that pediatric factors are not so important and might even lead pediatricians to think that they have already played their part in the fight against neonatal mortality. Autopsy series collected from maternity hospitals may give a somewhat misleading picture of the relative importance of the different causes of death, since sometimes only those infants are included who have died during the first few days after birth.[7-10]

It is true that the majority of neonatal deaths occur during the first week after birth but there is also an appreciable mortality rate during the next 3 weeks. Only if autopsies are performed on all the infants that die during the neonatal period in a given district can reliable data be collected, but very few such studies have been performed.[11] Investigations concerning the responsibility for neonatal deaths have indicated that pediatric factors are often involved.[12, 13]

Autopsy studies collected from a children's hospital provide additional information about the causes of neonatal deaths and shed further light on the pediatric problems involved. Such studies may enable the pediatrician in charge of sick newborn infants to learn which are the commonest fatal diseases at this early stage of life. Clinical diagnosis of the diseases of the newborn infants is not always easy.[14] When more than one disease is present, important symptoms may be overlooked. It may be helpful to know how often more than one disease is present as a cause of death during the neonatal period and what is the clinical relationship between the different diseases seen at autopsy. Since the causes of neonatal deaths have not been much investigated from the pediatric angle, it was considered that a study of these questions in the light of autopsy series collected from Finland's largest pediatric hospital would be of value.

MATERIAL AND METHODS OF CLASSIFICATION

The series consists of 1,247 infants who died at less than 1 month of age in the years 1947-1956, inclusive. They were mostly treated in the Helsinki Children's Clinic but some died in the Women's Clinic and autopsy was performed at the Pathologic Laboratory of the Children's Clinic. There were 674 premature infants (birth weight 600-2,500 grams) and 573 full-term infants (birth weight

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more than 2,500 grams). Table I shows the age distribution of the patients. Autopsy was performed in every case without restriction. After 1949, most organs were studied histologically, but even before that time microscopic examination was performed as indicated and the lungs, at least, were studied in most cases. Autopsy reports and case histories were reviewed during this study and all available information was used in estimating the cause of death.

TABLE I. DISTRIBUTION OF PATIENTS ACCORDING TO AGE AT DEATH

AGE AT DEATH IN DAYS	NO. OF PATIENTS		
	PREMATURE	FULL-TERM	TOTAL
Less than 1	96	71	167
1	120	61	181
2	76	67	143
3	53	48	101
4	45	34	79
5	44	32	76
6	31	23	54
Less than 7	465	336	801
7-13	119	111	230
14-29	90	126	216

Death was attributed to an anatomic cause wherever possible. In classification, the following principles were used. For example, when intracranial hemorrhage was present it was considered to be the underlying cause of death except when a severe malformation was also present. Malformations were listed as the cause of death when the malformation was severe enough to cause death either alone or in conjunction with some other factor. Infection was considered to be the underlying cause of death only when it was present without any other possible lethal factor. Hyaline membranes were considered as the primary cause of death only when they were the only significant pathologic observation or when they occurred in association with pneumonia or with pulmonary hemorrhage. Kernicterus occurring in conjunction with a severe malformation or with intracranial hemorrhage was not listed as the primary cause of death, since it seems probable that in such cases the malformation or the intracranial hemorrhage preceded the kernicterus. Anoxia was considered to be the cause of death when there were clinical and/or anatomic features consistent with it and there were no other changes which would have made it possible to include the case in some other group. The diagnosis of prematurity was reserved for cases in which there were no other findings and the infant was clinically and anatomically immature.

UNDERLYING OR PRIMARY CAUSES OF DEATH

The number and percentage distribution of deaths from various underlying causes are seen in Tables II and III. Intracranial hemorrhages are divided into two groups. Traumatic hemorrhage includes subdural

TABLE II. NUMBER OF NEONATAL DEATHS FROM DIFFERENT CAUSES

CAUSE OF DEATH	NO. OF PATIENTS		
	PREMATURE	FULL-TERM	TOTAL
Intracranial hemorrhage:			
Traumatic	39	46	85
Other	135	30	165
Other hemorrhages	30	21	51
Congenital malformations	93	230	323
Infections	138	109	247
Hyaline membranes	94	30	124
Kernicterus	67	44	111
Erythroblastosis	7	25	32
Anoxia	13	11	24
Prematurity	31	—	31
Miscellaneous	27	27	54
Total	674	573	1,247

hematoma, rupture of the tentorium or falx, rupture of the great vessels, and fracture of the skull. Other intracranial hemorrhages are leptomeningeal (subarachnoid) and intraventricular hemorrhages, and softening of the brain. These will be considered as nontraumatic or anoxic intracranial lesions. Traumatic hemorrhages form about one third of the whole group, which is the second largest in this series. Nontraumatic intracranial hemorrhages are commoner among premature than among full-term infants, as has been noted by others. Traumatic hemorrhages are "morphologically" traumatic but the nontraumatic etiology of some of the other hemorrhages may be questionable. Labor is often traumatic for a small premature infant and if leptomeningeal hemorrhage is found at autopsy in such a case it is hardly possible to prove that it was not caused by trauma and was due to anoxia. Even if it is accepted that leptomeningeal hemorrhages are caused by anoxia, and there is evidence indicating that they are, this does not exclude trauma as the cause of this type of hemorrhage.[15-17] Anoxia may play a part in the production of traumatic intracranial lesions. Since it was felt important to ascertain the number of cases in which intracranial hemorrhage was present, it was necessary to include all cases of intracranial hemorrhage and not only those in which there was a severe hemorrhage. This made it necessary to subdivide this group.

TABLE III. PERCENTAGE DISTRIBUTION OF DEATHS FROM DIFFERENT CAUSES

CAUSE OF DEATH	PERCENTAGE OF TOTAL		
	PREMATURE	FULL-TERM	TOTAL
Intracranial hemorrhage:			
Traumatic	6	8	7
Other	20	5	13
Other hemorrhages	4	4	4
Congenital malformations	14	40	26
Infections	20	19	20
Hyaline membranes	14	5	10
Kernicterus	10	8	9
Erythroblastosis	1	4	2.5
Anoxia	2	2	2
Prematurity	5	–	2.5
Miscellaneous	4	5	4

The category "other hemorrhages" comprises the cases in which there was a severe hemorrhage in some organ other than the brain. The commonest fatal hemorrhage was massive pulmonary hemorrhage (25 cases); in addition there were 14 cases of adrenal hemorrhage, 4 cases of hemoperitoneum caused by rupture of the liver, and 8 other hemorrhages—chiefly melena. Etiologically these cases can hardly be considered as belonging to the same group. Rupture of the liver and adrenal hemorrhage may be caused by trauma or anoxia.[18-22] The pathogenesis of large pulmonary hemorrhage is obscure. It is possible that different factors are responsible in different cases.[23] The cases of this group are similar only in the respect that fatal bleeding occurred. When classification on an anatomic basis is used, it is difficult to include these cases in any other group and for this reason they have been placed in a special category.

Congenital malformations form the largest group. As seen from Table IV, malformations of the gastrointestinal tract were the commonest type in this series. This is at variance with the incidence of different

types of malformation in other statistics and indicates that the series is a selected one.[1, 11, 18, 24-29] The selection is chiefly due to the fact that the Children's Clinic is the center of neonatal surgery for the whole country and infants with malformations needing surgical repair are sent there from the whole of Finland. The number of malformations is smaller in premature infants than in full-term infants, but if the incidence is calculated per birth and not per autopsy it is seen that premature infants have more malformations than full-term infants.

TABLE IV. DISTRIBUTION OF DIFFERENT TYPES OF MALFORMATION

TYPE OF MALFORMATION	NO. OF CASES		
	PREMATURE	FULL-TERM	TOTAL
Cardiac	24	56	80
Central nervous system	9	23	32
Gastrointestinal	41	114	155
Genitourinary	5	9	14
Multiple	9	26	35
Other malformations	2	2	4
Tumors	3	0	3
Total	93	230	323

Infections are fairly common as the underlying cause of death. Table V shows the distribution of the different types of infection. Pneumonia of newborn infants has been discussed earlier.[30] It is the commonest type of infection in most statistics. Both cases of congenital syphilis are from the earlier years and this disease is hardly any longer seen as a cause of death in Finland. The low number of meningeal infections indicates that the danger of infection in cases of intracranial hemorrhage is hardly as great as is sometimes asserted.[31]

TABLE V. DISTRIBUTION OF INFECTIONS BY LOCATION

LOCATION OF INFECTION	NO. OF CASES		
	PREMATURE	FULL-TERM	TOTAL
Pulmonary	74	43	117
Gastrointestinal	34	24	58
Cutaneous	6	7	13
Meningeal	2	6	8
Other locations	15	6	21
Septicemia	7	21	28
Syphilis	0	2	2
Total	138	109	247

Hyaline membranes were commoner than appears from the tables. Owing to the method of classification only some cases of membranes are included in the tables. The total number of hyaline membranes in this series was 318, of which 286 were seen in the infants who died during the first week of life. This number includes all the cases in which even slight membranes were found at histologic examination. The number of cases of well-developed hyaline membranes in the whole series was 222.

Kernicterus includes the cases with and without blood group incompatibility. Since serologic studies were not performed in all cases, and particularly not in the cases of the first years of this study, it was impossible to use any other method of classification. In a great number of the cases the Rh factor was not implicated. Erythroblastosis designates serologically confirmed cases excluding kernicterus.

The deaths from anoxia form a fairly small group. This is due to the method of classification. In none of the cases was anoxia confirmed chemically. Neonatal asphyxia or signs of fetal distress were mentioned in many case records but these notes are not sufficiently detailed to be

used in evaluating the role of anoxia as a cause of death in this series. According to the records, asphyxia was present at birth in 283 cases and was fairly evenly distributed among the different groups mentioned in Tables II and III.

When an attempt was made to divide the patients in the prematurity group into two different types, it was found that there were 22 cases in which the lungs were atelectatic and which could be called "abnormal pulmonary ventilation" and 9 in which the lungs were expanded. In the absence of other findings all these infants were assumed to have died from prematurity.

The category "miscellaneous" comprises cases in which death was due to overheating during transportation,* abnormalities of internal secretion, liver diseases, and 18 cases in which the cause of death was unknown.

IMMEDIATE CAUSE OF DEATH

In most studies on neonatal mortality, the underlying cause alone has been considered. Often, however, more than one factor has contributed to the death of the newborn infant. An analysis of immediate and underlying causes of death gives different information about these factors than one in which the underlying cause alone is studied.[11, 32] It was found during this investigation that study of the immediate cause of death supplements the knowledge gained when the underlying cause of death is studied. When the number of underlying and of immediate causes of death are compared in the largest groups, it is found that in about one fourth an underlying cause alone was present (Table VI). Many diseases which are often considered to be fatal to the newborn infant are associated with other diseases which may have contributed to the fatal end. This is especially seen in the groups of intracranial hemorrhages, malformations, and hyaline membranes.

TABLE VI. NUMBER OF DEATHS FROM UNDERLYING CAUSES ALONE AND FROM UNDERLYING AND IMMEDIATE CAUSES TOGETHER

UNDERLYING CAUSE OF DEATH	NO. OF CASES WITH UNDERLYING CAUSE ONLY	NO. OF CASES WITH UNDERLYING AND IMMEDIATE CAUSE
Intracranial hemorrhage	66	184
Other hemorrhages	36	15
Malformations	72	251
Hyaline membranes	68	56
Erythroblastosis and kernicterus	42	101
Total	284	607

Three groups will be inspected in some detail. Table VII shows the commonest immediate causes of death in these groups. The most common immediate cause of death was infection, which was present in 42 per cent (106/250) of cases of intracranial hemorrhage and in 67 per cent (219/323) of cases of malformation. Infection was seen in many other groups,

*Since it is very cold in Finland in winter, premature infants are transported in specially constructed wooden boxes with special hot water bottles. There is no automatic system of regulation of warmth in these boxes but the temperature of the infant is taken regularly. In these cases the person looking after the infant was not careful and there was too much heat which seemingly was followed by a severe hyperthermia of the infant —and death.

TABLE VII. NUMBER OF DEATHS FROM THE COMMONEST IMMEDIATE CAUSES

UNDERLYING CAUSE OF DEATH	IMMEDIATE CAUSE OF DEATH (NO. OF CASES)		
	OTHER HEMORRHAGES	INFECTIONS	HYALINE MEMBRANES
Intracranial hemorrhage	20	106	45
Malformations	24	219	4
Hyaline membranes	12	44	–
Total	56	369	49

too, and altogether it appeared as an immediate cause of death in 468 cases, excluding the cases in which infection complicated previous infection, as for example pneumonia complicating diarrhea. Infection was present as an underlying cause of death in 20 per cent and as an immediate cause of death in 36 per cent. The total number of infections was 715, so that it was present in 57 per cent of all cases as an underlying or as an immediate cause of death. The clinical significance of the infection may be questioned in several cases, but, on the other hand, many infants with malformation, intracranial hemorrhage, or some other debilitating disease finally succumb to infection, or infection makes surgical correction of a malformation impossible. The relationship between hyaline membranes and pneumonia is known and it has been stated that when an infant with hyaline membranes dies after 48 hours of age, pneumonia usually is present.[33] Table VIII shows the number and percentage distribution of deaths from pneumonia in cases with hyaline membranes when the cases with massive pulmonary hemorrhage are excluded. It is seen that pneumonia is often present even within the first 24 hours and may be absent later on. The incidence of pneumonia in association with hyaline membranes is about the same as the incidence of pneumonia in general at the same age, according to data published earlier.[30]

TABLE VIII. INCIDENCE OF PNEUMONIA IN CASES OF HYALINE MEMBRANES

AGE IN DAYS	NO. OF CASES	NO. WITH ASSOCIATED PNEUMONIA	PERCENTAGE
Less than 1	93	13	14
1	82	37	46
2	31	16	52
3	18	12	67
4	12	6	50
5	8	7	87
6	7	6	86

Hemorrhages other than intracranial were seen as an immediate cause of death in a total of 92 cases. They are thus more common as underlying causes than as immediate causes of death. It appears to be a matter of individual interpretation what is considered the mutual relationship between intracranial and pulmonary hemorrhage when they are seen in the same case. In this study, intracranial hemorrhage was considered to be the underlying cause of death. It is possible that both types of hemorrhage may be caused by the same factor or they may not be etiologically related at all. When a newborn infant has a malformation and in addition a massive hemorrhage, the latter occurred later and was perhaps partly caused by the malformation.[34] In many cases the relationship may be difficult to detect.

The whole number of hyaline membranes is greater than the number of hyaline membranes as an underlying cause and as an immediate cause of death taken together. This is due to the method of classification and can be seen to be true of several other anatomic features also.

CHANGES IN THE DISTRIBUTION OF DEATHS FROM DIFFERENT CAUSES

As would be expected, some changes in the number and percentage distribution of deaths from different causes have taken place during the period under study.[35] The changes in the age at death are seen in Table IX. When the first 3 year period is compared with the last 4 year period, it is seen that in the later years there are more deaths in the younger age groups. Changes in the number and percentage distribution of deaths from different underlying causes are seen in Tables X and XI. The total number of cases of intracranial hemorrhage per year has not changed much, but there has been a change in the type of these hemorrhages. The number of deaths from traumatic hemorrhages has decreased, whereas the number from nontraumatic hemorrhages has increased. There is an increase in the number of cases of congenital malformation. The yearly increase is so small, however, that this trend may be caused by the increase in the number of cases referred to the hospital. The improved training of the general practitioner and the increase in the number of pediatricians in the country are probably largely responsible for this increase in the number of cases of malformation referred to the Children's Clinic. No calculation has been made of the number of cases of malformation treated in the Children's Clinic during these years but it appears improbable that the mortality rate has increased. The number of infections has markedly decreased during the period under study. This is in accordance with clinical experience in the hospital and throughout the country. The relatively small number of cases of hyaline membranes in the first 3 year period as compared with the other periods may be partly due to the smaller number of infants referred to the hospital soon after birth in these years. During the first years of this study the Children's Clinic was more crowded than later on and no special ward was reserved for newborn infants. This may partly explain this change but it may partly be attributable to improved cooperation between obstetricians and pediatricians. In the other groups the changes are relatively small.

The changes in the most important immediate causes of death are seen in Table XII. The number of deaths

TABLE IX. DISTRIBUTION OF PATIENTS BY AGE AT DEATH AT DIFFERENT PERIODS

AGE AT DEATH IN DAYS	NO. OF CASES AT DIFFERENT PERIODS		
	1947-1949	1950-1952	1953-1956
Less than 1	25	53	89
1	39	67	75
2	36	42	65
3	39	22	40
4	30	28	21
5	33	18	25
6	18	11	25
Less than 7	220	241	340
7-13	102	43	85
14-29	121	44	51
Total	443	328	476

TABLE X. NUMBER OF NEONATAL DEATHS FROM DIFFERENT CAUSES AT DIFFERENT PERIODS

CAUSE OF DEATH	NO. OF PATIENTS								
	1947-1949			1950-1952			1953-1956		
	PREMATURE	FULL-TERM	TOTAL	PREMATURE	FULL-TERM	TOTAL	PREMATURE	FULL-TERM	TOTAL
Intracranial hemorrhage:									
Traumatic	22	14	36	12	20	32	5	12	17
Other	27	3	30	37	4	41	71	23	94
Other hemorrhages	15	2	17	8	10	18	7	9	16
Malformations	25	66	91	24	60	84	44	104	148
Infections	94	68	162	21	26	47	23	15	38
Hyaline membranes	13	3	16	32	14	46	49	13	62
Kernicterus	18	20	38	14	8	22	35	16	51
Erythroblastosis	1	6	7	1	6	7	5	13	18
Anoxia	2	4	6	4	2	6	7	5	12
Prematurity	15	–	15	10	–	10	6	–	6
Miscellaneous	18	7	25	5	10	15	4	10	14
Total	250	193	443	168	160	328	256	220	476

TABLE XI. PERCENTAGE DISTRIBUTION OF NEONATAL DEATHS FROM DIFFERENT CAUSES AT DIFFERENT PERIODS

CAUSE OF DEATH	PERCENTAGE OF TOTAL								
	1947-1949			1950-1952			1953-1956		
	PREMATURE	FULL-TERM	TOTAL	PREMATURE	FULL-TERM	TOTAL	PREMATURE	FULL-TERM	TOTAL
Intracranial hemorrhage:									
Traumatic	9	7	8	7	13	10	2	5	4
Other	11	1.5	7	22	2.5	13	28	10	20
Other hemorrhages	6	1	4	5	6	5	3	4	3
Malformations	10	34	21	14	38	26	17	47	31
Infections	38	35	37	13	16	14	9	7	8
Hyaline membranes	5	1.5	4	19	9	14	19	6	13
Kernicterus	7	10	9	8	5	7	14	7	11
Erythroblastosis	0.4	3	2	0.6	4	2	2	6	4
Anoxia	0.8	2	1	2	1	2	3	2	3
Prematurity	6	–	3	6	–	3	2	–	1
Miscellaneous	7	4	6	3	6	5	2	5	3

TABLE XII. NUMBER OF NEONATAL DEATHS FROM THE COMMONEST IMMEDIATE CAUSES AT DIFFERENT PERIODS

UNDERLYING CAUSE	IMMEDIATE CAUSE (NO. OF CASES)								
	OTHER HEMORRHAGES			INFECTIONS			HYALINE MEMBRANES		
	1947-1949	1950-1952	1953-1956	1947-1949	1950-1952	1953-1956	1947-1949	1950-1952	1953-1956
Intracranial hemorrhage	3	9	8	39	31	36	1	9	35
Malformations	5	5	14	60	54	105	0	1	3
Hyaline membranes	2	4	6	5	14	25	–	–	–
Total	10	18	28	104	99	166	1	10	38

with infection as an immediate cause in cases of intracranial hemorrhage has not changed, but the number of deaths from hyaline membranes in such cases has increased. This increase is also visible during that time when there was no increase in number of cases of hyaline membranes as an underlying cause of death. As mentioned above, there has been a simultaneous increase in the number of cases of nontraumatic intracranial

hemorrhage (Table X). Hyaline membranes are associated with traumatic intracranial hemorrhages in 23 per cent (20/85) of cases and with other (nontraumatic) intracranial hemorrhages in 42 per cent (69/165) of cases in this material.

It has been mentioned above that infection was common as the immediate cause of death in cases of malformation (Table VII). It can be seen from Table XII that their number has not decreased during the period under study and Table XIII indicates that when the number of these cases increased the incidence of infection as an immediate cause of death remained the same. It can be seen from Table XIV that the number of fatalities due to malformation without any immediate cause of death has not changed much.

TABLE XIII. INCIDENCE OF INFECTIONS AS IMMEDIATE CAUSE OF DEATH IN CASES OF MALFORMATION

PERIOD	NO. OF CASES	NO. WITH INFECTION	PERCENTAGE
1947-1949	91	60	67
1950-1952	84	54	64
1953-1956	148	105	71

TABLE XIV. NUMBER OF DEATHS DUE TO MALFORMATION WITH AND WITHOUT AN IMMEDIATE CAUSE OF DEATH AT DIFFERENT PERIODS

PERIOD	WITHOUT IMMEDIATE CAUSE	WITH IMMEDIATE CAUSE
1947-1949	25	66
1950-1952	23	61
1953-1956	24	124

DISCUSSION

It is not possible to take into account all the factors contributing to the death of newborn infants, when this mortality is studied on the basis of autopsy records and classification of the causes of death is made on an anatomic basis. Obstetric and social factors have not been studied but they are discussed in other papers.[1, 36-41] Even clinical factors and anatomic findings may be so numerous and so complex that some authors have considered it impossible to tabulate the causes of death of newborn infants.[42] Some questions, however, can be discussed in the light of an anatomic study such as that presented in this paper.

Intracranial hemorrhage has been studied more extensively than any other cause of death in the newborn infants. The incidence of this lesion varies greatly in different statistics and the evaluation of anatomic findings by different authors is not always the same. In many papers some types of intracranial hemorrhage have been included under the heading "anoxia" and this may profoundly affect the number of cases referred to this group. Nor is the method of classification similar in all studies in respect to either this point or many other points, which makes comparison difficult. The decrease in the number of severe—traumatic—hemorrhages and increase in small—possibly nontraumatic—hemorrhages seen during this study has been noted in some other series, too. It has been attributed to changes in obstetric procedure or to the use of vitamin K.[16, 43] Finnish obstetricians report that they have changed their methods during the last 10 years, performing cesarean sections in preference to using forceps.[44] If all intracranial hemorrhages are considered to be caused by trauma, it seems possible that this change to the less traumatic

methods in the conduct of labor explains the change in the ratio of these types of hemorrhage. If this is indeed the explanation, real progress has been made, and one is glad to believe that this is the case. But if leptomeningeal and intraventricular hemorrhages are thought to be caused by anoxia, it is questionable whether it is of any benefit if the infants now die of or show the sequelae of anoxic, rather than traumatic, brain damage. It has already been mentioned that it is hard to exclude the possibility that part of the leptomeningeal hemorrhages are caused by trauma. On the other hand, many pathologists think that intraventricular and leptomeningeal hemorrhages are due to anoxia.[45-48] There is some evidence in favor of this view.

In the present study, it was found that the minority of patients with an intracranial hemorrhage had this lesion alone. It was further found that there was a simultaneous increase of nontraumatic intracranial hemorrhages and hyaline membranes and that hyaline membranes were more commonly associated with nontraumatic than with traumatic hemorrhages. This raises the question of the mutual relationship between these two diseases when seen in the same patient. Patients with hyaline membranes are clinically anoxic. At autopsy they have an increased amount of subdural fluid,[18] which may indicate that the membranes have some effect on the brain. It might be suggested that in some cases hyaline membranes are the underlying cause of death, leptomeningeal and intraventricular hemorrhage being partly brought about by anoxia resulting from the presence of the membranes. The present series does not afford sufficient evidence to substantiate this hypothesis but it would partly explain the changes observed in the two types of intracranial hemorrhage. It is also possible that hyaline membranes and intracranial hemorrhages are caused by the same factor in these cases.

The practical conclusions to be drawn from the finding of an increase in the number of deaths from immediate causes simultaneously with the change in the ratio of the types of intracranial hemorrhage are that when newborn infants are treated, other diseases in addition to the hemorrhage should be looked for. Prevention and treatment of these "additional diseases" may help to save some of these infants.

Cases of large hemorrhages in organs other than the brain form a fairly small and etiologically heterogeneous group. The condition is seen more often as an immediate than as an underlying cause of death. Since these hemorrhages are included in different groups in other statistics, it is not possible to compare their incidence with that in other series. There is hardly any general measure for the prevention or treatment of these hemorrhages. A tendency to bleeding is only one factor in their genesis. The questions connected with the origin of these different types of hemorrhage will not be discussed but some types of hemorrhage are probably preventable and some are amenable to treatment.[49, 50]

The number of cases of congenital malformation has increased markedly in this series during the period under study. It cannot be concluded

from this that there is any increase in the incidence of congenital malformation in Finland. It seems probable that more cases are referred to the hospital now than in the past and that more cases are diagnosed. The increasing proportion of congenital malformations in newborn infants that die in the neonatal period indicates that they are becoming more and more important to the pediatrician. Apart from giving the patients the best possible care little can be done to lower the mortality rate due to malformations. In some of these cases surgical correction is feasible. An almost essential condition for this is that the patient has no infection and does not develop infection postoperatively. In the present series malformation was complicated by infection in two thirds of cases and the surgeon may be right in claiming that these deaths were partly due to pediatric failure in spite of adequate surgical care. From the data of this study it is not possible to calculate how many deaths could have been prevented by elimination of infection but it can be seen that more should be done. This is in accordance with everyday experience in the treatment of malformations. Many infants with atresia of the gastrointestinal tract do not tolerate operation, since they already have an infection or contract one postoperatively. In the majority of cardiac malformations it would have been impossible to prevent a fatal outcome by treatment of the infection since the malformation was not compatible with life but some cases could have been treated successfully later.[51] The treatment of cardiac decompensation is sometimes beneficial and may help to lower the mortality rate among these cases.[52, 53] Without doubt, there are still many malformations of various organs which cannot be corrected and there is no chance of saving all the patients of this group, but it seems possible to reduce the mortality rate among them.

Although one cannot hope to prevent or treat successfully all cases of malformation, theoretically it seems possible to eliminate infection as a cause of neonatal death. The number of deaths from this cause has markedly decreased but infections are still seen as an underlying cause of death in rather less than one tenth of the cases of this series. The same trend is seen in most other mortality statistics based on autopsy series. In the mortality statistics, infections are usually studied as underlying causes only and may be stated to be disappearing. This study indicates that if infections as an immediate cause of death are taken into account, they are found to play a far more important role. It was further seen that infections as an immediate cause of death are not decreasing in number, although they have decreased as an underlying cause of death. Hence, it can be concluded that infection is still a real risk to a newborn infant, especially when he has some other disease. The finding that nowadays infection is as common an immediate cause of death as it was 10 years ago may give rise to the pessimistic view that it is not possible to reduce this cause of neonatal death with the methods now available. This study does not supply an answer to the

question of how frequently the infants were already infected on admission and how often infection was contracted in the hospital.

Hyaline membranes are one of the commonest causes of neonatal death. The expression "abnormal pulmonary ventilation" has been widely used instead of this anatomic diagnosis. Since in this study classification was made on an anatomic basis as far as possible, the anatomic diagnosis was preferred. I agree with the statement that there are disadvantages in the use of such indefinite terms.[54] It is better if the clinician tries to make as exact a diagnosis as possible and can see from the mortality statistics the number of different anatomic findings. Not all the cases of hyaline membranes are seen in the tables. They were present in about 25 per cent of all the infants but it is probable that only in some of these cases were they important as a cause of death. They were regarded as an underlying cause of death, i.e., they were present almost alone, in 10 per cent. When hyaline membranes are seen concurrently with some other disease it is not easy to explain the mutual relationship between the membranes and the other disease. This point has been discussed above in connection with intracranial hemorrhages. It has also been found that hyaline membranes and pneumonia may be associated at any age. When pneumonia and hyaline membranes are seen together in the lungs of a newborn infant, one cannot always conclude that pneumonia was caused by the membranes. This statement must not be taken to imply that the use of antibiotics in patients exhibiting symptoms of hyaline membranes should be omitted. The relationship between hyaline membranes and massive pulmonary hemorrhage needs further study.

The number of cases of kernicterus in this material is high. In the years following this study their number has decreased but they have not disappeared. It is probable that some of the cases of this series were induced by overdosage of vitamin K and in earlier years sulfonamides were an etiological factor. Kernicterus without blood group incompatibility is still seen in premature infants, however. The treatment of these cases has been discussed in several recent papers.[55]

The percentage of anoxia given as a cause of death varies very greatly in different statistics. This variation is due more to differences of opinion than to differences in the actual findings. Since classification was mainly anatomic in the present study, cases of anoxia form a small group.

The information available regarding the present series was not always sufficient to permit a reliable estimate of the degree of asphyxia during labor or at birth. Hence anoxia could not be used as a basis of classification. It is quite possible that many diseases presented in the tables as underlying causes of death result from anoxia. There is no doubt that anoxia is an important etiological factor in many neonatal diseases and may lead to death either alone or with additional factors. Anoxia has been considered to be an important etiological factor in intracranial hemorrhages, hemorrhages of other organs, pneumonia, hyaline membranes, and kernicterus. If all these cases,

or the majority of them, had been included in the category "anoxia," the size of this group would have increased greatly.

Prematurity is given as the cause of death more often in statistics made without adequate autopsies than in those based on autopsy series. Small premature infants die without doubt of prematurity alone but in most cases anatomic changes can be found in the organs. The difference in the number of deaths from prematurity alone in different periods of this study is probably due to differences in the adequacy of the autopsies. Prematurity is an important factor among the causes of death, but in attempts to find methods to lower neonatal mortality it is necessary to define the cause of death as exactly as possible. So many other factors besides the changes observed at autopsy affect the mortality of premature infants, however, that this question requires special study.

When the causes of neonatal deaths are surveyed in the light of all the information gained from this study, it is seen that the death of the newborn infant is often attributable to more than one disease. It is not possible in every case to determine the causal relationships between these diseases. It is possible that anoxia is one of the most important single factors in the etiology of neonatal deaths, and this should be borne in mind when many diseases of newborn infants are considered. Because of the complex nature of the question it is impossible to foresee whether and to what extent the neonatal mortality could be reduced, but it is felt that there are causes of death which should be preventable when they are studied in the light of autopsy findings. It seems possible to reduce the mortality in every group discussed in this paper. There are cases of congenital malformation which are not preventable and not curable, but in every other group there appear to be no limits to the possibility of reducing the number of cases. It is quite another matter how far this will prove possible in clinical practice and what methods should and can be used.

SUMMARY

The causes of neonatal deaths have been studied in the light of an analysis of a consecutive autopsy series of 1,247 infants who died at less than 1 month of age. There were 573 full-term and 674 premature infants. Underlying cause and immediate cause of death were taken into account. In the classification of the cases, anatomic causes of death were chiefly used, but clinical histories were also taken into consideration. The distribution of deaths from these different causes in different stages of the 10 year period under study was compared. The commonest underlying causes of death were malformations, infections, intracranial hemorrhages, hyaline membranes, and kernicterus. The commonest immediate causes of death were infections, hyaline membranes, and large hemorrhages in organs other than the brain. Infection was present as an underlying or immediate cause of death in more than half of the cases. During the period under study the number of cases of malformation increased while those of infection decreased as an underlying cause of

death. The total number of intracranial hemorrhages increased only a little but within this group an increase in the number of cases of nontraumatic hemorrhage and a decrease in those of traumatic hemorrhage were found. No change was seen in the incidence of infection as the immediate cause of death in cases of malformation and intracranial hemorrhage. The number of cases of intracranial hemorrhage in which hyaline membrane was an immediate cause of death was found to have increased. There was a relative increase in the younger age groups simultaneously with these changes in the distribution of the causes of death.

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MYOCARDIAL INFARCTION IN THE PERINATAL PERIOD

Report of Two Cases in Newborn Infants

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MYOCARDIAL infarction and coronary artery disease in the neonatal period have been reported many times, both as an idiopathic lesion and associated with well-recognized disease entities. In a review of some of our material and the pertinent literature, it appears that this disease may not be suspected frequently enough by the clinician or by the pathologist and as a result the cases are not studied thoroughly. Pre- and postmortem studies regarding possible etiologies of these pathological changes are strikingly scarce.

This report is presented for its clinical and pathological interest and to emphasize the need for more extensive studies. It should also indicate that myocardial infarctions and coronary artery disease in the neonatal period are more common than is generally believed.

CASE REPORTS

Case 1.—This 6 pound 9 ounce (3,000 gram) female infant was born of a gravida iii, 32-year-old white woman who has 2 normal children. The mother had an uncomplicated prepartum course and entered for delivery in active labor, the cervix fully dilated, and discharging meconium-stained fluid. Fetal heart sounds were barely perceptible and the mother was delivered rapidly under gas-oxygen-ether anesthesia. The cord was around the neck and the child was cyanotic but responded to resuscitation and oxygen within 2 minutes.

Physical examination of the infant after delivery showed the child to be completely normal with no cyanosis or cardiac abnormalities recorded. The infant was placed in 40 per cent oxygen in the pediatric nursery. She became cyanotic, however, and examination disclosed a low-pitched, rumbling, Grade 3 systolic cardiac murmur over the entire precordium with a maximum at the left sternal border. The second heart sound was inaudible in the aortic area and the femoral pulses were present but weak. There were no signs of failure, and an electrocardiogram taken at this time was reported as "consistent with congenital heart disease."

The baby's condition deteriorated and respirations became labored and grunting. Despite administration of 0.1 mg. digitoxin intramuscularly she became progressively cyanotic and died at the age of 15 hours and 9 minutes.

At autopsy (A56-51) the heart was enlarged to 28 grams (expected 20 grams) but no anomalies were noted. Except for generalized congestion there were no significant gross abnormalities in any of the other organs. Complete bacterial and viral studies were unproductive.

On microscopic examination of the heart an infarction of the tip of a papillary muscle of the mitral valve

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Fig. 1.

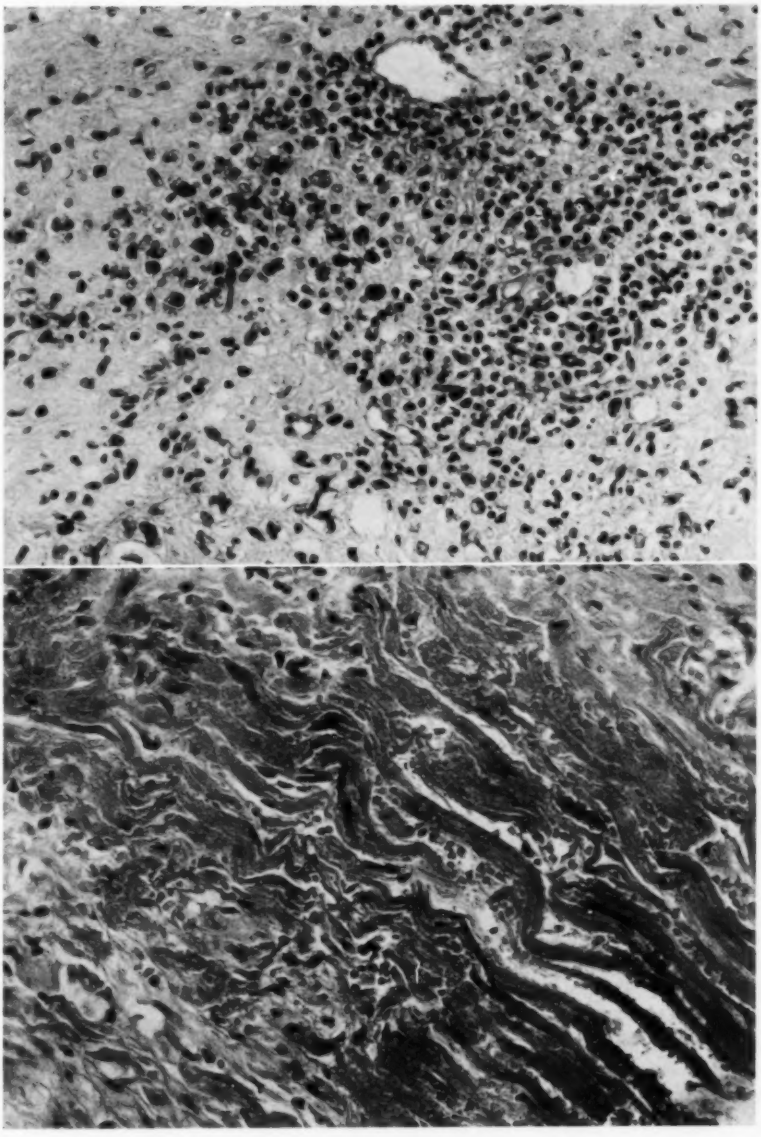

Fig. 2.

Fig. 1.—Section through tip of papillary muscle with large numbers of pigment-laden macrophages and inflammatory cells. (Hematoxylin and eosin. ×430; reduced ¼.)

Fig. 2.—Section through muscular tip of chorda tendinea of mitral valve. Note necrosis with calcification of myocardial fibers. (Hematoxylin and eosin. ×430; reduced ¼.)

was incidentally discovered in one section. The muscle fibers lacked striations, stained brick red with eosin, and appeared homogeneous. They were well demarcated from surrounding unaffected muscle. There was moderate hyalinization in the area with large numbers of pigment-laden macrophages inter-mixed with lymphocytes and phagocytes and a few polymorphonuclear leukocytes were present (Fig. 1). A second section through an atrioventricular valve included a chorda tendinea with its muscular tip in which the muscle was completely necrotic and contained calcific deposits (Fig. 2). There was no accompanying inflammation. There was no mural thrombus, and the epicardium, endocardium, and coronary vessels appeared normal in all sections examined. The only other finding of note was the presence of significant hematopoiesis and hemosiderosis in the liver. There were several small old and recent infarcts in the placenta.

CASE 2.—The mother of this infant was a 22-year-old gravida i who was normal on physical examination, blood group O, Rh negative, with a negative Hinton test. The pregnancy was uncomplicated, without illnesses and with a total weight gain of 21 pounds. The patient went into labor spontaneously at term and, after 13 hours of labor and artificial rupture of the membranes, a 6 pound 6 ounce (2,900 gram) female infant was delivered by low forceps under gas-oxygen-ether anesthesia. The umbilical cord was wrapped tightly twice around the baby's neck, ruptured during delivery, but was clamped immediately and no significant blood loss was noted. At the time of delivery meconium was noted. The placenta was normal on gross examination.

The child cried immediately and breathed spontaneously and regularly. There was no icterus, cyanosis, edema, or cardiac murmur. The baby progressed satisfactorily for 4 days and then began to have breath-holding spells and became lethargic. Her condition deteriorated and a grayish pallor and tense fontanelles were noted.

Subdural and spinal taps produced clear fluid containing two lymphocytes and 70 mg. per cent protein. A chest film at this time showed an enlarged left heart with no specific configuration. The lung fields were clear. An electrocardiogram showed right auricular hypertrophy and an intraventricular conduction defect. During the next 24 hours the infant developed cyanosis below the nipples with pallor of the head and shoulders, absent peripheral pulses, a gallop rhythm, a Grade 2 systolic murmur, and an enlarged liver. The infant was given 0.2 mg. digitoxin but she soon died at the age of 7 days.

At autopsy (A56-14) the infant's weight was 2,700 grams and the crown-rump measurement was 37 cm. The external appearance of the body was as described above. On opening of the body cavities the only grossly abnormal change observed was in the heart which was hypertrophied to 39 grams (expected 17.9 grams) but otherwise appeared normal. The coronary arteries were not remarkable and the great vessels were anatomically normal. On opening the left ventricle the endocardium had the sclerotic, pale appearance typical of subendocardial fibroelastosis. The left ventricle measured 1.7 cm. in thickness and the right ventricle 0.4 cm. There was a definite reddish mottling in the interventricular septum and the left ventricular wall.

On microscopic examination of the heart there was focal thickening of the endocardium with the deposition of numerous elastic lamellae. There was one small area of myocardial necrosis in the right ventricle with complete absence of round cell infiltration or capillary dilatation. Scattered diffusely throughout the interventricular septum and the anterior left ventricle were areas of myocardial infarction with varying appearance (Fig. 3).

Most of these appeared to be of recent origin and were accompanied by hemorrhage, polymorphonuclear infiltration, and abundant cellular debris, but several areas were almost devoid of an inflammatory response. In these areas the myocardial fibers stained brick red with eosin, and there was loss of striations. Other microscopic findings included focal acute bronchopneumonia, early acute leptomeningitis, chronic passive congestion of the liver, and acute and chronic ileitis with erosions. The bones and endocrine organs were within normal limits.

Although rupture of the papillary muscle was not appreciated grossly, we feel this probably occurred, in view of the striking absence of a murmur at birth and the subsequent onset of cyanosis concurrently with the presence of a loud systolic murmur. There was no evidence of failure or anemia. The coincidental findings of cyanosis, systolic murmur, and the concomitant rapid deterioration of the patient appear most consistent with the infarc-

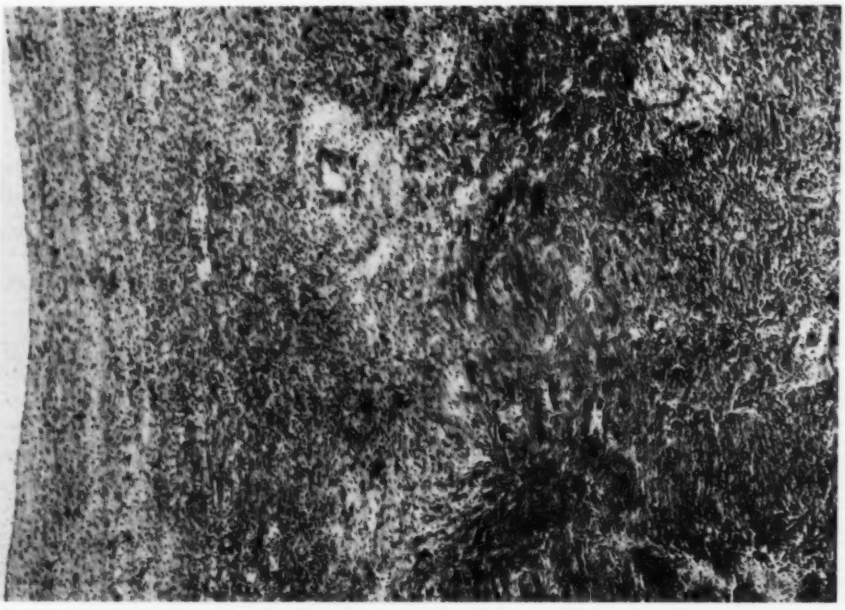

Fig. 3.—Section from left ventricle. Note thickened endocardium with large areas of myocardial necrosis. (Hematoxylin and eosin. ×30; reduced ⅙.)

DISCUSSION

Case 1 is of considerable interest in that a myocardial infarction was not suspected either clinically or by the prosector. There was no coronary artery disease noted either grossly or microscopically, and the etiology of the infarction is undetermined.

tion of a papillary muscle in utero and its rupture shortly after birth. This may have been precipitated by the sudden cardiac stresses of extrauterine life. The valvular distortion and hemodynamic changes of such a lesion would lead to cardiovascular decompensation and death.

We have found three previous reports of papillary muscle infarctions in infants but none led to separation of the muscle. In Ravich and Rosenblatt's[1] Case 2 there was infarction of the entire posterior left ventricle and the posterior papillary muscle of the mitral valve. There was no abnormality of the coronary arteries except for "many blood vessels . . . occluded by thrombotic material and whose walls merge with the surrounding necrotic tissue." These thrombi may well have been secondary to the infarction since both arteries and veins were involved and no underlying coronary artery disease was demonstrated. Edwards[2] mentioned a case of infarction in the posterior papillary muscle of the left ventricle of a child with coronary arteritis as a part of a rheumatic pancarditis. There was no evidence of rheumatic activity in our cases. In a case of Stryker's[3] there was subendocardial infarction and papillary muscle infarction associated with coronary artery calcification. The coronary arteries in our cases were not abnormal. The possibility that the lesion in these cases was due to viral or bacterial agents, though not excluded, is reduced by appropriate cultures taken at the time of autopsy.

In contradistinction to the present Case 1 with an infarction of undetermined etiology, most cases previously reported in the literature fall into one of several categories but most of them are the result of coronary occlusion. The etiologies of perinatal myocardial infarctions can be discussed in the framework of Stryker's[4] classification of coronary occlusions: (1) medial calcification with fibroblastic proliferation, (2) periarteritis, (3) atherosclerosis, (4) syphilitic arteritis, (5) embolism, (6) congenital anomalies, (7) rheumatic arteritis, and (8) hypertension.

There have been several reports of rheumatic myocarditis[5, 6, 7] and syphilitic arteritis[8] producing infarctions in the neonatal period and childhood. The clinical diagnosis here can be suspected frequently from the history, physical examination, and appropriate laboratory tests, and the etiology is understood.

The congenital anomalies of aberrant coronary arteries and subendocardial fibroelastosis associated with myocardial infarctions are frequently difficult to distinguish on clinical grounds. The excellent article by Rosenbaum and associates[9] discusses clinical differentiation. Our Case 2 showed the typical lesions found in subendocardial fibroelastosis with myocardial infarction.

Edwards[2] pointed out the pathologic physiology of aberrant left coronary arteries originating from the pulmonary artery acting as an A-V shunt and producing myocardial fibrosis due to hypoxia. Gross,[10] Craig,[11] and others[13] have written excellent reviews of subendocardial fibroelastosis. The etiology of myocardial infarctions in progeria as mentioned by Rosenthal and co-workers[12] is as poorly understood as the syndrome itself.

While classically thought of as a disease of adults, atherosclerosis has been well recognized in young people[14] and in the neonatal period.[15, 16] Fangman and Hellwig[17] examined the hearts of 30 newborn infants by careful histologic sections of the three main coronary arteries and found thickening of the intima with "cushionlike" elevations up to one-half the diameter of

the vessel, most frequently in the anterior descending vessel. They also described changes in the internal elastic lamina and fine lipoid deposits in the stroma of the "cushions." Shornagel[18] studied the anterior descending coronary artery in 87 infants less than 1 year of age and found that intimal hyperplasia was present frequently after the age of 1 month. He quotes Moschowitz[19] as stating that "the evolution of hyperplastic arteriosclerosis begins at birth as an irreversible process of adaptation." Nestor and his associates[20] reported the case of a Negro baby who succumbed from myocardial disease due to arteriosclerosis of the myocardial vessels at the age of 22 months (Case 1).

We have been unable to find a case of myocardial infarction in a perinatal infant attributable to a complication of hypertension and, although the infant was hypertensive in the case reported as healed polyarteritis by Dawson and Nabarro,[21] it cannot be determined that this contributed to his death.

A case reported by Ramsay and Crumrine[22] may have been an infarction due to embolization or it may have been of infectious origin. A well-defined case of infarction in a newborn infant due to embolization has not been described to our knowledge.

The majority of infarctions reported in the neonatal period have been associated with medial calcification and intimal hyperplasia. Such cases have been reported by Boldero,[24] Baggenstoss and Keith,[25] Stryker,[3] and others[26, 27] Traisman and collaborators[28] delineated the pathogenesis of the disease in their report of 50 cases of calcification of the coronary arteries in infants, and Rosenbaum[9] discussed the aids to clinical diagnosis. The etiology of this syndrome remains obscure and even though many papers have been written on the subject there has been very little information in many of them regarding the multiple suggested etiologies. These include parathyroid disease, renal disease, bone disease, primary disturbance in the calcium-phosphate metabolism and hypervitaminosis D, and a familial "poor protoplasm."

There is surprisingly little clinical information available in most protocols and, in those cases which came to autopsy, organ systems other than the cardiovascular system have been mentioned briefly, if at all. Simple laboratory determinations such as of serum calcium, phosphorus, alkaline phosphatase, vitamin D level, electrolytes and, in autopsied cases, careful examination of the endocrine system (including the parathyroid glands), kidneys, and bones would be helpful in attempting some correlations that may contribute to an understanding of this disease.

Finally, there is the puzzling group of infarctions with minimal or absent coronary artery disease and no obvious predisposing cause. This last group is exemplified by the present Case 1 and by the case of Kambolis, Lebhar, and Barnett[23] with thrombosis in the right coronary artery and intimal and medial thickening in the left coronary artery. The etiological factors here are obscure.

SUMMARY

Two cases of myocardial infarction in the neonatal period are presented with autopsy findings. In one of these the cause of death was circulatory insufficiency due to necrosis and probable

rupture of a papillary muscle. The second was associated with severe subendocardial fibroelastosis.

A review of the pertinent literature is presented.

Suggestions are made for further study of the entities discussed.

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STUDIES IN SPONTANEOUS HYPOGLYCEMIA IN CHILDHOOD

Failure to Increase the Epinephrine Secretion in Insulin-Induced Hypoglycemia

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SPONTANEOUS hypoglycemia with the dramatic symptoms which characterize this condition may occur in a great variety of disorders of varying etiology and pathogenesis. Recently Conn and Seltzer[1] in an etiological classification of this condition have listed more than 30 different causes. In many patients with spontaneous hypoglycemia a careful clinical workup may give evidence of some organic or functional lesion initiating the hypoglycemic attack, but there are also cases with unrecognizable etiology which are classified as idiopathic. Such a syndrome occurring in early childhood, i.e., idiopathic spontaneous hypoglycemia in infancy, has been extensively studied by McQuarrie and his associates.[2]

It is well established that adrenal cortical insufficiency may give rise to spontaneous hypoglycemia. Since, however, as demonstrated by von Euler and Luft,[3] the urinary excretion of epinephrine in normal adults rises to more than five times the initial value in insulin-induced hypoglycemia, probably as a compensatory mechanism, the possibility exists that a functional failure of the adrenal medulla may be responsible for inadequate balance between all those factors controlling the blood sugar level. To test the validity of the urinary epinephrine excretion in insulin-induced hypoglycemia, 3 children with spontaneous hypoglycemia of the idiopathic type and one child with hypoglycemic attacks due to hyperplasia of the beta cells of the pancreas have been investigated. In order to learn whether children react in the same way as adults, 5 normal healthy children have also been studied.

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MATERIAL

Idiopathic Hypoglycemia.—

Case 1.—K. J., a boy born in 1949, weighed 2,000 grams at birth, with a normal delivery.

There were endocrine disorders in the family. During the first 3 years of life on three different occasions the boy had generalized convulsions in connection with fever which were consequently regarded as simple febrile convulsions. He was admitted to the hospital for the first time at 5 years of age with an attack of unconsciousness and generalized clonic seizures. A blood sugar value of 42 mg. per cent was recorded during the attack. Hypertonic glucose was administered intravenously and he responded promptly. During the following 3 years he had repeated attacks of the type described above, which followed a short period of vomiting and drowsiness. During his many stays in the hospital we had

the opportunity of studying the course of the attacks: after a short period of drowsiness and vomiting, he suddenly became unconscious and within another few minutes had generalized clonic seizures. Tachycardia, flushing, and sweating were not observed during the initial phase. During the attacks we often recorded blood sugar levels of about 40 mg. per cent. The attacks always disappeared when hypertonic glucose was given intravenously. Prolonged starvation induced blood sugar levels as low as 50 mg. per cent. The insulin tolerance test (0.1 U. insulin per kilogram of body weight) produced a curve with a steep fall to 30 mg. per cent after only 14 minutes and released a hypoglycemic attack. The glucose tolerance curve (initial level 121 mg. per cent) showed a rise to 170 mg. per cent after 30 minutes and returned to levels well below the initial one within 90 minutes. Measuring of the urinary catechol excretion showed no increase in the urinary epinephrine excretion in insulin-induced hypoglycemia. Repeated tests gave the same result. Further investigation disclosed no signs of hypophyseal, thyroid, hepatic, or adrenal cortical dysfunction. Since the last examination the boy has been given ephedrine, 10 mg. daily, and has been completely free from hypoglycemic symptoms.

CASE 2.—S. E., a twin girl, was born in 1954. She weighed 1,450 grams. Delivery and development were normal.

Since the age of 18 months the girl has had several attacks of unconsciousness and general clonic seizures lasting for about one hour. The attacks occurred early in the morning before the first meal. In April, 1957, at an age of 2½ years she was admitted to the hospital for an investigation. Glucose tolerance test and insulin tolerance test were not performed and although the EEG was normal she was regarded as having epilepsy and was given antiepileptic treatment. On September 22, at the age of 2 years and 8 months, she was admitted to the children's clinic, Karolinska Sjukhuset, with an acute attack of unconsciousness and generalized clonic seizures which had started one hour earlier. On admission the girl was still unconscious and had generalized clonic seizures in periods of 2 minutes' duration. The blood sugar level was 40 mg. per cent and she was immediately given an intravenous infusion of hypertonic glucose. The attack subsided after a few minutes and cleared up completely. The neurological examination disclosed nothing abnormal. She had a normal EEG. Investigation of the hypophyseal, thyroid, hepatic, and adrenal cortical function revealed normal conditions. The oral glucose tolerance test (initial value 114 mg. per cent) showed a curve with a peak to 142 mg. per cent within 15 minutes and a return to the initial value after 30 minutes, whereafter the curve within 60 minutes declined to levels of about 90 mg. per cent. Repeated insulin tolerance tests gave blood sugar levels as low as 25 mg. per cent within 30 minutes and always gave rise to a hypoglycemic attack of the type described above. Insulin-induced hypoglycemia (repeated tests) did not increase the urinary epinephrine excretion.

Since September, 1957, the girl has been treated with daily doses of ephedrine and has not had any further attacks.

CASE 3.—P. F., a boy born in 1953, weighed 2,600 grams. Delivery was normal. The mother and a maternal aunt are slightly hypothyroid; otherwise there are no endocrine disorders in the family.

On the third day of life the boy had two attacks of cyanosis and clonic seizures. A thorough neurological examination disclosed nothing abnormal, but nevertheless the event was looked upon as the result of a slight birth injury. His development

has been normal both physically and mentally, however, and electroencephalographic examinations, performed yearly, have never given evidence of a cerebral lesion.

At 2 years of age he was hospitalized with his first hypoglycemic attack, during which a blood sugar value as low as 20 mg. per cent was recorded. The attack which stopped immediately on intravenous infusion of glucose, started with a short period of vomiting followed by unconsciousness and generalized clonic seizures.

During his first stay in the hospital the thyroid, hepatic, and adrenocortical functions were thoroughly investigated, but nothing abnormal was found. Since he had several hypoglycemic attacks during the following 6 months it was considered necessary to examine the pancreas. On operation the organ looked normal macroscopically and no insulomas could be palpated. Because a diffuse hyperplasia of the beta cells could not be excluded, half of the pancreas was resected. A microscopic examination of the resected part, however, did not reveal any signs of a hyperplasia of the beta cells.

During the following 3 years he had three further attacks of the same type as the initial one. In October, 1958, he was admitted to the pediatric clinic of the University of Gothenburg for further investigation. The oral glucose tolerance test showed a curve with a sharp peak to 200 mg. per cent (initial value 65 mg. per cent) after 30 minutes and a return to the initial value after 130 minutes. The epinephrine test (0.2 mg. of epinephrine intramuscularly) gave a prompt response with a rise from 70 to 130 mg. per cent within the first hour and a further rise to 187 mg. per cent after 2 hours. The insulin tolerance test (0.1 U. insulin per kilogram of body weight) gave a curve with a steep fall within 20 minutes to 43 mg. per cent from an initial blood sugar value of 82 mg. per cent. During the following 60 minutes the blood sugar gradually sank to 37 mg. per cent whereafter it rose in 10 minutes to values well above the initial one. The insulin-induced hypoglycemia did not increase the urinary excretion of epinephrine more than 18 per cent. No clinical signs of transient hyperadrenalism in the form of flushing, sweating, tachycardia, or rise in blood pressure could be recorded during the hypoglycemic phase.

The boy has been kept on a dose of ephedrin of 5 mg. twice a day since November, 1958, and has not had any further attacks.

Hyperinsulinism Due to Hyperplasia of the Beta Cells of the Pancreas.—

Case 4.—G. B. A., a girl, was born in 1948 by normal delivery.

The mother developed diabetes mellitus 2 months after the delivery. During the neonatal period the girl had repeated attacks of asphyxia which were considered to be due to a cerebral lesion although she lacked definite neurological evidence of such a disorder. During the following 2 years she was in excellent condition, but since 1950 she has had several attacks of unconsciousness with generalized clonic seizures, some of them lasting for more than one hour. A thorough neurological investigation gave no evidence of epilepsy. The EEG was normal and an air encephalogram revealed nothing abnormal. Antiepileptic treatment did not decrease the intensity or frequency of the attacks which occurred most often when the girl had not eaten for several hours.

In 1956 a diagnosis of hypoglycemia was established. The acute attacks could be provoked by prolonged starvation, when blood sugar levels as low as 25 mg. per cent) were recorded, and responded promptly to treatment with hypertonic glucose. The glucose tolerance curve (initial level 115 mg. per cent) showed a high

peak, up to 200 mg. per cent, within 15 minutes, returning to levels of about 130 mg. per cent, with a steep fall to 70 mg. per cent after 2 hours. The insulin tolerance curve (0.1 U. insulin per kilogram of body weight) with an initial blood sugar level of 95 mg. per cent showed a successive fall to 40 mg. per cent after 90 minutes, when the girl had a convulsive attack with unconsciousness. In the initial phase we could observe a rise in the blood pressure, tachycardia, flushing, and sweating. Insulin hypoglycemia increased the urinary epinephrine excretion fivefold. Further investigation disclosed no insufficiency of the hypophyseal, thyroid, hepatic, or adrenal cortical function.

As the attacks became more and more severe we decided in 1957 to perform a laparotomy and explore the pancreas. On operation the organ appeared macroscopically normal. Insulomas could not be seen or palpated. A subtotal resection of the organ was performed. Microscopic examination of the resected part gave clear evidence of a diffuse hyperplasia of the beta cells.

The postoperative course was uncomplicated. The girl was completely free from symptoms during the next 6 months but since then she has had two attacks of unconsciousness and clonic seizures of relatively short duration. These attacks did not respond to treatment with hypertonic glucose and could not be provoked by prolonged fasting. The glucose tolerance and the insulin tolerance tests were normal. These later attacks were probably not due to hypoglycemia but were the result of cerebral damage caused by the repeated and prolonged hypoglycemia, as has been suggested by McQuarrie and coworkers.[2]

The case is reported to illustrate a well-established case of hyperinsulinism due to diffuse hyperplasia of the beta cells with a normal urinary epinephrine excretion after insulin-induced hypoglycemia.

None of the children in the hypoglycemic group or the control group has shown any impairment of renal function.

METHODS

The Insulin Tolerance Test.—The patient was kept fasting overnight. At 9 A.M. insulin in a dose of 0.1 U. per kilogram of body weight was injected intravenously. Capillary blood samples were taken 10, 20, 30, 45, 60, 75, 90, 120, 150, and 180 minutes after the injection. Blood sugar was estimated according to the method described by Hagedorn, Halstrøm, and Norman Jensen.[4]

Pulse rate and blood pressure were determined at 10 minute intervals.

Estimation of the Epinephrine and Norepinephrine Excretion.—The bladder was emptied with a catheter at 6 A.M. The urine was collected between 6 A.M. and 9 A.M. as the control period (sample 1) and during the insulin tolerance test from 9 A.M. to 12 noon (sample 2). The urine was adjusted immediately after sampling to pH 3.5 and norepinephrine and epinephrine were estimated with the fluorimetric method described by von Euler and Floding.[5] The catecholamines are oxidized at pH 3.5, where only a small per cent of the norepinephrine is oxidized and the epinephrine is completely oxidized. At pH 6 both catecholamines are completely oxidized, and the oxidized products adrenochrom and noradrenochrom are then transmitted to the corresponding trihydroxyindol derivative, which can be estimated fluorimetrically.

RESULTS

As seen in Table II, in the 3 patients with idiopathic hypoglycemia

TABLE I. BLOOD PRESSURE, PULSE RATE AND BLOOD SUGAR LEVELS

AGE (YEARS)	SEX	BLOOD PRESSURE (MM. Hg)		PULSE RATE (PER MIN.)		BLOOD SUGAR (MG. PER 100 ML.)	
		BEFORE INSULIN	AFTER INSULIN	BEFORE INSULIN	AFTER INSULIN	BEFORE INSULIN	AFTER INSULIN
Patients With "Idiopathic Hypoglycemia."—							
3	F	100/60	60/-	82	120	107	25
8	M	120/70	100/70	70	90	100	50
5	M	100/70	105/85	84	88	82	37
Patient With Hyperinsulinism.—							
10	F	100/60	120/80	70	120	105	60
Control Patients.—							
1 1/12	F	110/80	130/90	86	126	105	71
1 5/12	F	90/60	105/75	105	130	100	69
2 6/12	M	100/50	120/65	76	115	108	57
7	F	90/60	115/70	72	100	107	80
8	F	95/50	110/65	75	110	123	64

TABLE II. URINARY EXCRETION OF CATECHOLS

AGE	SEX	EPINEPHRINE (μG PER MIN.)		NOREPINEPHRINE (μG PER MIN.)		PER CENT EPINEPHRINE OF TOTAL CATECHOLS	
		CONTROL PERIOD	INSULIN PERIOD	CONTROL PERIOD	INSULIN PERIOD	CONTROL PERIOD	INSULIN PERIOD
Patients With "Idiopathic Hypoglycemia."—							
3	F	0.0070	0.0030	0.0025	0.0040	74	43
8	M	0.0027	0.0029	0.0058	0.0054	31	35
5	M	0.0057	0.0067	0.0047	0.0070	55	49
Patient With Hypoglycemia Due to Hyperinsulinism.—							
10	F	0.0027	0.0135	0.0107	0.0152	25	47
Control Patients.—							
1 1/12	F	0.0045	0.0212	0.0062	0.0101	37	68
1 5/12	F	0.0035	0.0160	0.0023	0.0030	60	84
2 6/12	M	0.0035	0.0833	0.0027	0.0027	57	97
7	F	0.0066	0.0283	0.0038	0.0038	58	88
8	F	0.0028	0.0658	0.0013	0.0177	68	85

the urinary epinephrine excretion did not increase in insulin-induced hypoglycemia, while in the case of hyperinsulinism due to hyperplasia of the beta cells of the pancreas and the 5 control cases the excretion was increased five- to twentyfold. The results are in full agreement with those obtained by von Euler and Luft[3] in their examination of normal adults.

It is noteworthy that the 3 children with idiopathic hypoglycemia during the initial phase of the insulin-induced hypoglycemia had no symptoms which could be attributed to a compensatory transient hyperadrenalism. The girl with hyperplasia of the beta cells of the pancreas and the 5 children in the control group, on the other hand, developed increased blood pressure and pulse rate and sweating and flushing which may be consistent with a transient hyperadrenalism.

COMMENT

Investigations by several authors have yielded evidence that hypoglycemia following administration of insulin elicits an increased excretion

from the suprarenal medulla. In view of the glycemic action of epinephrine, this effect may be regarded as the manifestation of a blood-sugar-regulating mechanism, as has been stated by Duner.[6]

In normal children the urinary epinephrine excretion rose to the same degree as has been observed in adults. Furthermore, the response in the child with spontaneous hypoglycemia due to hyperinsulinism from hyperplasia of the beta cells of the pancreas was also quite normal. In these children, however, with hypoglycemia classified as idiopathic, the increase in the epinephrine excretion in the urine was very low or completely lacking. It seems reasonable to assume that there is, in these patients, a connection between the severe and dramatic attacks of spontaneous hypoglycemia and the failure of the adrenal medulla to respond to insulin-induced hypoglycemia in a normal way. Evidence for such a suggestion also emerges from the fact that all three patients seem to have responded favorably to continuous ephedrine treatment. In this connection it may be relevant to discuss the pathogenesis of the symptomatology seen in hypoglycemia since it has been suggested that at least some of the symptoms may be due to transient adrenal medullary hyperfunction induced by hyperinsulinism.

In the 3 cases of idiopathic hypoglycemia described above, which we had the opportunity to study carefully during the acute hypoglycemic attacks, there were never any symptoms which could be attributed to hyperadrenalism. Flushing, sweating, tachycardia, or rise of the blood pressure could not be observed in the initial phase of the attacks but could be observed in the case of hyperinsulinism due to hyperplasia of the beta cells of the pancreas and in the control cases. A careful observation of the symptoms during the acute attacks may therefore give an indication as to whether the hypoglycemia could be due to a functional failure of the adrenal medulla.

SUMMARY

Three cases of idiopathic hypoglycemia in childhood with no increase in the epinephrine secretion in insulin-induced hypoglycemia are reported. The possibility of hypofunction of the adrenal medulla as the cause of the hypoglycemic attacks is discussed. This theory is supported by the fact that all 3 children have been completely free from symptoms after continuous ephedrine medication. To test the validity of the theory one child with hyperinsulinism due to hyperplasia of the beta cells of the pancreas and 5 normal children of various ages were investigated with regard to their excretion of epinephrine after injection of insulin.

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DIURNAL SERUM TRIGLYCERIDE LEVELS OF CHILDREN WITH CYSTIC FIBROSIS OF THE PANCREAS

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A NUMBER of investigators have observed a decrease in the absorption of dietary fats with consequent hypolipemia in children with cystic fibrosis of the pancreas.[1-7] Recently, Holman[8] reported a low incidence of aortic atherosclerosis in children who died of the disease and its complications.

The nutritional pattern of children with fibrocystic disease of the pancreas is similar in certain respects to that of peoples subsisting on diets deficient in animal fats and proteins. The incidence of atherosclerosis is known to be low among such undernourished peoples.[9-13]

The fasting and diurnal serum triglyceride concentrations in children with cystic fibrosis of the pancreas were investigated in view of the following observations: (1) the incidence of clinical atherosclerosis is better correlated with serum triglyceride concentration than with serum cholesterol levels, (2) the fat and carbohydrate contents of each meal can produce prompt and marked changes in the serum triglyceride level, and (3) a neutral fat lipemia develops with fat restriction.

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MATERIAL AND METHOD

Clinical Data.—Nine children from 3¾ to 15 years of age with cystic fibrosis of the pancreas who had moderate to severe degrees of malnutrition were admitted to St. Christopher's Hospital for Children for study.

The pertinent clinical data on these 9 children are summarized in Table I. Seven other children including 3 with mental retardation and convulsive disorders and 4 who were convalescing from minor surgical procedures, between the ages of 2¾ and 9 years, were similarly studied as controls. A brief summary of the clinical data of children in the control group is presented in Table II.

Diets and Blood Samples.—The study period is divided into two parts: (a) with and (b) without the administration of pancreatic extract. During the period of study these children received a mixed diet which supplied from 1,200 to 1,600 calories per day and contained approximately 40, 16, and 44 per cent of fat, proteins, and carbohydrates, respectively. In addition 1 Gm. per pound of body

TABLE I. CLINICAL DATA OF PATIENTS WITH CYSTIC FIBROSIS OF THE PANCREAS

NAME	SEX	AGE (YEARS)	WEIGHT (POUNDS)	HEIGHT (INCHES)	DUODENAL ENZYME	SWEAT CHLORIDE (mEq./L.) (NORMAL MEAN 35 mEq./L.)	PULMONARY PATHOLOGY	FASTING BLOOD SUGAR (MG. %)
M. J. M.	F	6	33	44½	Neg.	238	+	56
G. C.	F	5	35	41	Neg.	110	+	56
M. J.	F	5	33	41	Neg.	148	+	64
C. O.	M	10	52	51	Neg.	151	+	81
R. K.	M	8½	43	48	Neg.	150	+	65
W. S.	M	15	63	60	Neg.	140	+	66
F. G.	M	8½	38	46	Neg.	136	+	54
T. M.	M	8	54	49	Neg.	112	+	70
J. V.	F	3¾	26¾	36	Neg.	125	+	62

TABLE II. CLINICAL DATA OF CONTROL PATIENTS

NAME	SEX	AGE (YEARS)	DIAGNOSIS	WEIGHT (POUNDS)	HEIGHT (INCHES)	FASTING BLOOD SUGAR (MG. %)
S. A.	F	5	Burn of back	40	42	68
S. M.	M	5	Bronchiectasis	42	43	62
J. K.	F	3	Mental retardation	24	35	48
W. L.	M	3	Legg-Perthes disease	39	35	63
A. G.	F	6	Dislocation of hip	40	45	62
B. A. K.	F	9	Convulsive disorder	44	49	62
P. H.	F	2¾	Convulsive disorder	40	33	59

weight of predigested protein (Amigen*) and 2 to 3 Gm. per pound of weight of Dextrimaltose* were given with each meal. No feedings, other than the regular meals served at 8 A.M., 12 noon, and 4 P.M., were allowed. Venous blood samples were drawn before each meal and every 4 hours thereafter over 24 hours for blood lipid determinations. A second 24 hour blood lipid test was performed on each of the children 7 to 10 days after the start of 1.5 Gm. of pancreatic extract three times a day.

Laboratory Methods.—Total serum cholesterol, phospholipid, and triglycerides were measured in each sample of blood. The methods of Abell, Levy, Brodie, and Kendall,[14] of Zilversmit and Davis,[15] and of Van Handel and Zilversmit[16] were used for the respective determinations. The triglyceride values obtained from each 24 hour test were utilized to plot a diurnal serum triglyceride curve.

*Supplied by Mead Johnson & Company, Evansville, Ind.

RESULTS

Diurnal Serum Triglyceride Curves of Children With Cystic Fibrosis of the Pancreas.—The individual and mean diurnal serum triglyceride levels of 9 children with cystic fibrosis of the pancreas are shown in Fig. 1. The fasting serum triglyceride values (8 A.M. sample) of these children ranged between 52 and 112 mg. per cent with a mean of 81 mg. per cent. No apparent correlation between the nutritional status and the fasting serum triglyceride concentration could be established among the children studied. A study of the pattern of these curves

revealed the following characteristics: (1) the serum triglyceride levels of all the children showed a slight rise from their respective early morning levels (12 P.M. to 4 A.M.) with prolonged fasting (16 hours); (2) except for minor fluctuations, the postprandial portions of the curves of these patients were quite flat and low; (3) in all instances the curves dipped to their respective nadirs between 12 P.M. and 4 A.M.

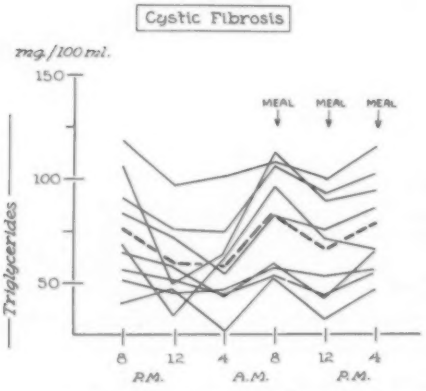

Fig. 1.—Diurnal serum triglyceride curves of 9 children with cystic fibrosis of the pancreas. The mean of these curves is represented by the broken line.

Diurnal Serum Triglyceride Curves of Children in the Control Group.—The diurnal serum triglyceride curves of 7 children with supposedly normal pancreatic functions are presented in Fig. 2. The mean fasting (8 A.M. sample) serum triglyceride concentration of these children was 87 mg. per cent with a range of 44 to 115 mg. per cent. These figures approximate closely those obtained from children with cystic fibrosis of the pancreas. The patterns of the diurnal variations in serum triglyceride concentrations of the two groups of children were quite different, however.

In contrast to the children with cystic fibrosis of the pancreas, the serum triglyceride curves of the children in the control groups were characterized by (1) moderate to marked lipemic rises during the postprandial periods (8 A.M. to 8 P.M.), (2) progressive lowering of the levels when no further food was taken after supper (8 P.M to 8 A.M.) and (3) dipping to their respective low or lowest levels following 16 hours of fasting.

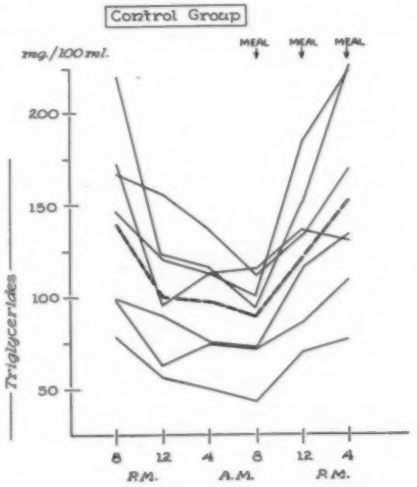

Fig. 2.—Diurnal serum triglyceride curves of 7 children with presumably normal pancreatic function. The mean of these curves is represented by the broken line.

Effect of Pancreatic Extract Upon the Serum Triglyceride Concentrations of Children With and Without Cystic Fibrosis of the Pancreas.—Administration of pancreatic extract did not produce a significant alteration in the diurnal serum triglyceride levels of the 7 children in the control group. The diurnal variations in serum lipid levels of W. L., a 4-year-old boy with Legg-Perthes disease before (solid line) and after (dotted line) Viokase

administration are presented in Fig. 3. His total serum cholesterol levels did not appear to be significantly influenced by ingestion of food, whereas his serum phospholipid level tended to rise following ingestion of food in each situation. Except for minor variations, his diurnal serum triglyceride patterns obtained without and with administration of Viokase were essentially unchanged.

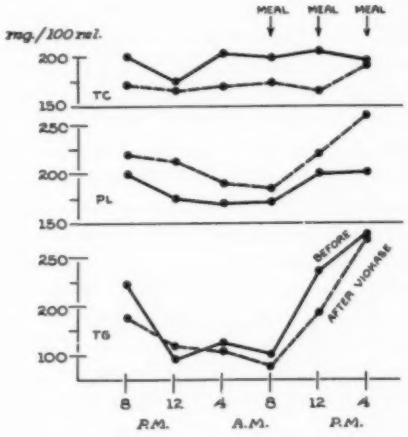

Fig. 3.—Diurnal total serum cholesterol (*TC*), phospholipid (*PL*), and triglyceride (*TG*) curves of W. L. with normal pancreatic function. Each set of curves represents determinations made before (solid line) and during (broken line) Viokase administration.

The serum triglyceride curves of 6 of the 9 patients with cystic fibrosis of the pancreas were changed toward a more normal pattern during the time when pancreatic extract was administered. Fig. 4 shows the serum lipid studies obtained from R. K., a 9-year-old child with severe cystic fibrosis of the pancreas who manifested such a response. There were no significant changes in the serum total cholesterol and phospholipid levels in relation to meals with (dotted line) or without (solid line) administration of Viokase. However, administration of pancreatic extract promptly changed the low and flat diurnal serum triglyceride curve to the more normal U- or V-shaped pattern (dotted line) suggestive of a significant increase in the absorption of dietary fat.

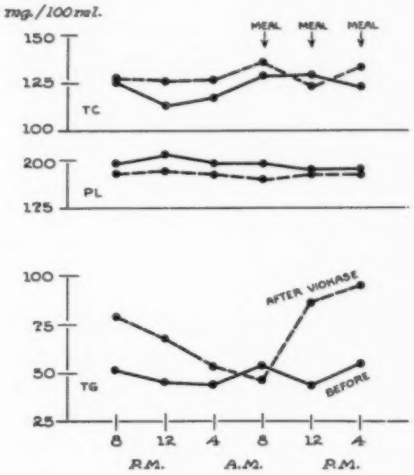

Fig. 4.—Diurnal total serum cholesterol (*TC*), phospholipid (*PL*), and triglyceride (*TG*) curves of R. K. with cystic fibrosis of the pancreas and severe malabsorption syndrome. Each set of curves represents measurement made before (solid line) and during Viokase (broken line) administration.

The effect of pancreatic extract upon the mean diurnal serum triglyceride curve of the 9 children with cystic fibrosis of the pancreas and of the 7 normal controls is summarized in Fig. 5. In the control group, serum triglyceride curves obtained before and after Viokase administration were almost identical. Pancreatic extract appeared to be able to promote an increase in triglyceride absorption in some of the children with cystic fibrosis of the pancreas. In those cases, following administration of Viokase the low and flat W-shaped serum triglyceride curve

was changed to a U- or V-shaped pattern, but the levels throughout the postabsorptive periods were 15 to 20 mg. per cent lower than those of the controls.

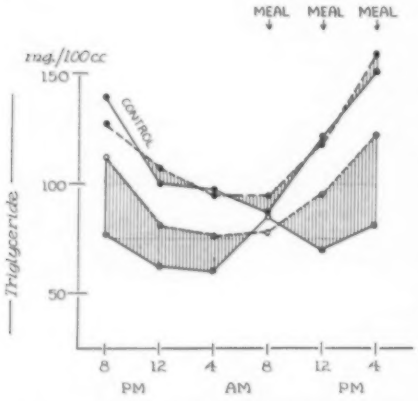

Fig. 5.—Mean diurnal serum triglyceride curves of the control (black dots) and cystic fibrosis (open circles) groups before (solid lines) and during (broken lines) pancreatic extract therapy. Hatched areas indicate increases in serum triglycerides following Viokase administration.

Serum Cholesterol and Phospholipid Levels.—In none of the children in either group was there any consistent variation in the diurnal curves of serum cholesterol. The mean total serum cholesterol concentrations of the patients with cystic fibrosis of the pancreas and of the children in the control group were 124 and 175 mg. per cent, respectively. The mean serum phospholipid concentrations of the two groups were 165 and 180 mg. per cent, respectively. A small postprandial rise in serum phospholipids was observed in 5 of the 7 children in the control group and in 3 of the 9 children with cystic fibrosis of the pancreas following administration of Viokase.

DISCUSSION

A variety of test meals have been utilized to study the digestion and absorption of fat.[17-19] In children with cystic fibrosis of the pancreas limited postabsorptive increases in the serum lipid concentration suggestive of impairment of absorption of fat from the test meals have been observed.[2, 4-7] Since it has been shown that both fat and carbohydrate contents of each meal consistently produce profound effect upon the postprandial absorption and deposition of fat and the resultant serum triglyceride level,[20-24] a comparative study of the serum lipid pattern of children with cystic fibrosis of the pancreas and that of normal children consuming a mixed diet seemed desirable. In the present study this purpose was achieved by maintaining the children on three regular meals and measuring the diurnal variations in their serum lipid levels.

The naturally imposed restriction of fat in patients with cystic fibrosis of the pancreas offers a unique condition for the study of the effects of a low-fat diet upon serum lipid levels. Liberal amounts of Amigen and of Dextrimaltose were given to each of our patients to promote more adequate protein and carbohydrate absorption in the face of the severe deficit in absorption of fat. This experimental design thus creates in these children with cystic fibrosis of the pancreas a condition closely similar to that of patients who have for one reason or another been placed on a low-fat diet.

Hatch,[25] Ahrens,[26] and Albrink[27] and their associates observed that a number of patients would exhibit a neutral fat lipemia (elevated serum triglyceride) following severe restriction of their daily intake of dietary fat. Although the serum triglycerides of our children with cystic fibrosis of the pancreas did show a small rise with prolonged fasting from the very low

levels observed during the early hours of fasting, the range and mean values of this fasting blood lipid fraction were essentially the same in the diseased children and in the controls. This finding is in accord with the recent observation of Kuo and Carson[28] that, in a nonhyperlipemic subject, the fasting serum triglyceride level was not significantly affected by the use of a very low-fat diet. By contrast, in a hyperlipemic patient, the fasting serum triglyceride level may show a considerable elevation when such a patient is maintained on a rice diet.

In this study, the mean serum cholesterol and phospholipid levels of children with cystic fibrosis of the pancreas were found to be only slightly lower than those of the children in the control group. The postprandial lipemia attained by the two groups was strikingly different, however (Fig. 5). The possibility of an association between the postprandial hypolipemia and the decreased incidence of aortic atherosclerosis observed in patients with cystic fibrosis of the pancreas[8] is a subject for speculation. It is interesting to note, however, that Albrink and Man[27] recently reported a good correlation between a high serum triglyceride concentration and a relatively high incidence of clinical atherosclerosis.

SUMMARY

1. Diurnal serum lipid variations of 9 children with cystic fibrosis of the pancreas and of 7 children with presumably normal pancreatic function as controls have been studied in relation to mixed diets before and during the administration of pancreatic extract. Serum triglycerides, phospholipid, and cholesterol concentrations were determined at intervals of 4 hours for periods of 24 hours.

2. Little or no variations in the diurnal serum cholesterol and phospholipid patterns were observed in the two groups of children. In the control and diseased children, the mean serum cholesterol concentrations were 175 and 124 mg. per cent, respectively, and the phospholipids were 180 and 165 mg. per cent, respectively.

3. The diurnal serum triglyceride curves of children with cystic fibrosis of the pancreas differed from those of the children in the control group in the following ways: (1) little or no postprandial rise, (2) a moderate dip in the early hours of fasting, and (3) a slight rise with prolonged fasting.

4. Significant but modest postprandial increases in the serum triglyceride levels were observed in 6 of 9 children with cystic fibrosis of the pancreas during the administration of Viokase.

5. Despite the naturally imposed restriction of fat by children with cystic fibrosis of the pancreas, none of the patients in this series had a neutral fat hyperlipemia. The mean fasting serum triglyceride concentration of the patients was essentially the same as that of the children in the control group.

6. The possibility of an association between the low diurnal serum triglyceride levels and the decreased incidence of aortic atherosclerosis in children with cystic fibrosis of the pancreas is a subject for speculation and further correlative studies.

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A NEW ELECTROCARDIOGRAPHIC OBSERVATION IN CRETINISM

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CRETINISM remains one of the most eminently treatable diseases in medicine, and its amenability to therapy is dramatized by the disastrous consequences of neglect of treatment. This is almost invariably due to failure to diagnose the condition, since unfortunately not all cretins have the classical stigmas of macroglossia, umbilical hernia, mottled skin, and coarse appearance, especially during the first few months of life. Use of the protein-bound iodine (PBI) and radioactive iodine (I^{131}) uptake tests and the myxedema reflex[1] have recently enhanced the facility of making the correct diagnosis. Any other examination that might be of diagnostic help would, of course, be welcome. Intrigued by the presence of apparent right ventricular hypertrophy in the precordial electrocardiogram of a cretin (Case 1) in whom this sign rapidly disappeared during therapy, we were prompted to examine the electrocardiograms of other cretins.

MATERIAL

Cases diagnosed as cretinism at the Ochsner Clinic and at the Louisiana State University School of Medicine (and Charity Hospital in New Orleans) were reviewed and 7 were found to have had electrocardiograms suitable for study. In addition to typical clinical manifestations, the diagnosis in all cases was confirmed by PBI or I^{131} tests (or both). In one patient (Case 3) these tests were initially blocked by the previous administration of Lipiodol during examinations for presenting macroglossia at a time when cretinism as a diagnosis had not been entertained; this child's deep tendon reflex was diagnostic of myxedema at that time (before therapy) and one year later, when she was not receiving thyroid hormone which had been discontinued by her mother. Her PBI in an untreated phase was 2.9 μg per cent. Data regarding all 7 cases are presented in Table I.

RESULTS

Electrocardiograms from 6 of the 7 cases are reproduced in Figs. 1 through 6. In the seventh patient, first examined in 1947 at the age of 5 years, the electrocardiogram consisted of the three standard bipolar extremity leads plus precordial Lead V_4. As this tracing was preserved only on microfilm, a satisfactory photograph could not be obtained for this report. Examination of it through a microfilm reader showed complete right bundle branch block, total QRS duration being 0.13 second.

In Cases 1 to 5 a pure or predominant R wave was recorded in V_1

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TABLE I. SUMMARY OF CLINICAL AND LABORATORY DATA IN 7 CASES OF CRETINISM

CASE NO.	AGE	RACE	SEX	24 HOUR I^{131} UPTAKE (15-45%*)	SERUM PBI (4-88%*)	ALKALINE PHOSPHATASE (5-12 BODANSKY UNITS*)	PLASMA[1] TSH LEVEL (0-0.5 μG/ML.*)	COMMENTS
1.	3 months	W	M		3.1 (7.6)†	2.3	10.0 (<2.5)†	Typical physical findings
2.	3 months	W	F	—	1.0	2.9		Anemic, jaundiced in first week of life[30]
3.	3 months	W	F	—	(2.9)‡	2.9		Typical myxedema reflex
4.	30 months	N	M	2.0	1.5	2.7 (11.5)†	5.0	Untreated when first seen
5.	13 months	N	M	—	1.5	3.8 (8.7)†	8.0	Typical physical findings
6.	5 months	W	M	<2.0	2.8	—	—	Had received small doses of thyroid since age of 3 months. Jaundiced first 2 months of life
7.	5 years	W	F	—	(3.3)†	—	—	Had received inadequate doses of thyroid since age of 5 months, stopped for 1 year at age of 3½ years. ECG on microfilm showed RBBB

*Normal ranges with a tadpole method.[31]
†Values after treatment.
‡Determination one year later while not receiving thyroid hormone.

with a considerable delay in the onset of the intrinsicoid deflection in 3 of the 5 (Figs. 1-3). Complete right bundle branch block was demonstrated in Cases 6 and 7 (Fig. 6). We did not observe any peculiarity at the S-T segment, such as has been described by others.[6, 7]

DISCUSSION

Since delayed excitation of the right ventricle was demonstrated in the electrocardiograms of 5 of the 7 cretins examined before treatment, this observation may be characteristic of cretinism in infancy. Previous observers[2-7] who conducted electrocardiographic studies on cretins, employing 3 lead tracings, concluded that the tracings are characteristic of hypothyroidism only in the same fashion as the electrocardiograms of adults with myxedema, that is, that they show low QRS and T voltage which increases after treatment with thyroid. Since the unipolar precordial leads are essential for the accurate diagnosis of ventricular hypertrophy, or bundle branch block, it is not surprising that the older studies do not refer to them.

Evidence for reversibility with treatment, which seems apparent in our Cases 1 and 5, must be confirmed by further observation, for this is an age

during which some diminution in R potential of V_1 occurs in normal children within a few months.[8] For this reason electrocardiograms made more than a few months after institution of therapy may show changes due either to therapy or to normal evolution of the infant's heart.

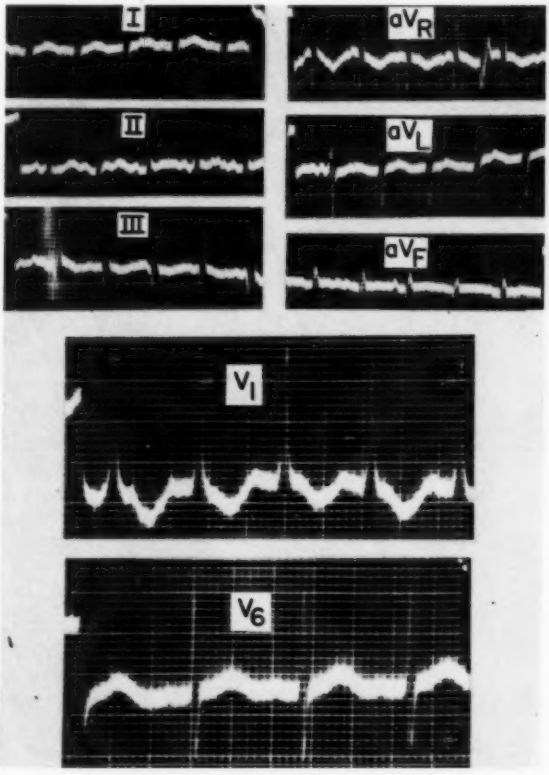


Fig. 1A.—Case 1. Electrocardiogram before treatment, at age of 3 months. This and all subsequent electrocardiograms were made at conventional paper speed (25 mm. per second) and standardization (10 mm. per millivolt). The enlargement of V_1 and V_6 is for the sake of clarity regarding the intrinsicoid deflection. The intervening V leads are omitted for brevity; they were made in each case and showed the expected progression of R/S relationship.

Delayed right ventricular excitation may be irreversible in some cases. One of our patients (Case 7) had been treated, though intermittently and inadequately, since the age of 5 months; yet at the age of 5 years complete right bundle branch block was demonstrated on the electrocardiogram. We do not have an electrocardiogram after therapy in Case 6, in which there was also right bundle branch block. In Case 3 the electrocardiogram before treatment exhibited an almost pure R wave in V_1, with the time of intrinsicoid deflection measuring 0.04 second; after therapy for 2½ years the S wave was deeper in V_1 but the R wave was just as tall as it was before treatment, and the time of intrinsicoid deflection was still 0.04 second.

One consideration regarding pathogenesis of these electrocardiographic changes is that children of this age group normally have tall R waves over the right precordium. They do not ordinarily, however, have an intrinsicoid deflection in V_1, which is delayed beyond 0.03 second.[8] As noted earlier, 5 of our 7 patients had either considerably delayed R waves in V_1 or right bundle branch block. The other 2 patients (Cases 4 and 5) had tall R waves in V_1, measuring 11 and 12 mm., respectively, but the intrinsicoid deflection was only 0.02 or a fraction more. Because of the R/S ratio in V_1, however, we believe these 2 cases also represent preponderant right ventricular potential.

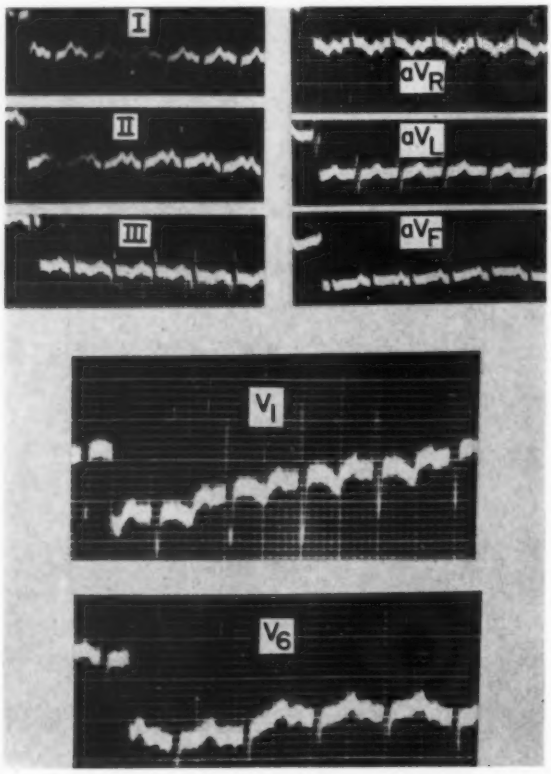


FIG. 1*B*.—Case 1. Electrocardiogram after 2 months of treatment with thyroid extract. The intrinsicoid deflection in V_1, which was 0.04 second before, is now 0.02 second, and the amplitude of R is diminished from 16 to 8 mm. There has been a corresponding shift in the electrical axis in both the bipolar and unipolar extremity leads.

The possibility of true right ventricular hypertrophy was investigated. Adults with myxedema frequently have arterial hypertension,[9, 10] the arteriolar resistance in these patients is increased,[11, 12] and the peripheral arterioles of cretins also behave abnormally.[13] Perhaps in infants with the right ventricle predominant analogous

abnormal pulmonary arteriolar resistance and consequently right ventricular hypertrophy might develop. We discarded this theory for several reasons. First, the roentgenograms in the tracings of all 10 patients before and after therapy with thyroid are clearly reproduced. In their Cases 1, 3, 4, 6, and 10, there does not appear to be any actual reduction in QRS

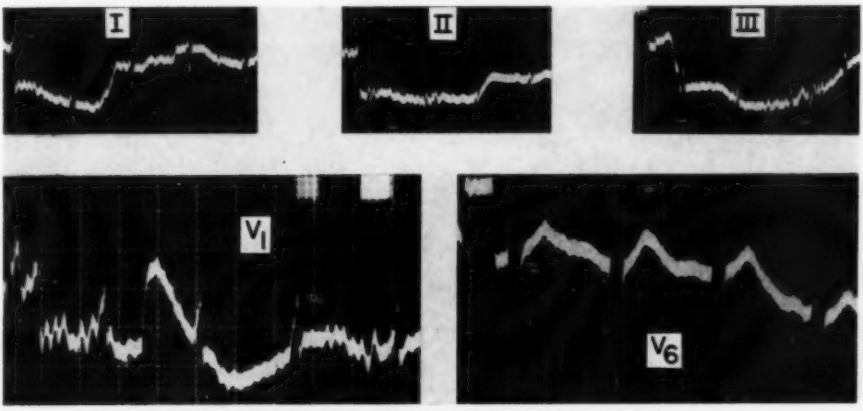


Fig. 2.—Case 2. Electrocardiogram before treatment, at the age of 3 months. Intrinsicoid deflection in V_1 is 0.04 second; right axis deviation is present in the bipolar limb leads. No subsequent tracings were available.

our patients did not show prominence of the main pulmonary artery as they should with pulmonary hypertension (Fig. 7). Second, review of necropsied cases of newborn infants with aplasia or hypoplasia of the thyroid[14] revealed 7 with hearts of normal size and one with generalized cardiac hypertrophy in association with atrioventricularis communis and dextroposition of the great vessels, and incidentally pulmonary emphysema. Finally, review of the few reported necropsies performed on cretins[15-19] failed to disclose any case in which right ventricular hypertrophy was described.

During the course of our studies we became acquainted with the fascinating report by Korth and Schmidt[20] describing delayed right ventricular excitation in the precordial electrocardiograms of 10 adults with myxedema; duration after treatment, and the change in R/S relationships after treatment may have been due to change in electrical axis of the heart. In Cases 2, 5, 7, 9, and probably 8, however, there seemed to be an actual reduction in QRS duration, and the complexes before treatment probably did represent right bundle branch block, as the authors interpreted.

Korth and Schmidt postulated that the right ventricle suffers more than the left in any systemic disease; they specifically cited beriberi, amyloidosis, and hemochromatosis. They believed that the same delayed right ventricular excitation could be found in all of these disorders if proper search were made, and additionally referred to observing the same delay in their patients with thyrotoxicosis. This latter

observation, which they noted was reversible by treatment of the thyrotoxicosis, was identical with that in the adults with myxedema where it was reversible by administration of thyroid extract. This they considered to be conclusive evidence that the delayed right ventricular excitation characteristic of adults with untreated myxedema is not a unique result of the hypothyroidism but a nonspecific effect on the right ventricle manifested by a variety of systemic diseases, including hyperthyroidism.

A measure of support for the observations of Korth and Schmidt is provided by the electrocardiograms published by Zondek[21, 22] in his classic papers first describing the heart in myxedema. His tracings unfortunately consist, as did all electrocardiograms then, of only the three bipolar limb leads. In his first report[21] Lead I in 2 cases showed a broad S wave and wide QRS suggesting right bundle branch block in both instances. In his second report[22] the electrocardiograms of 3 cases were published and

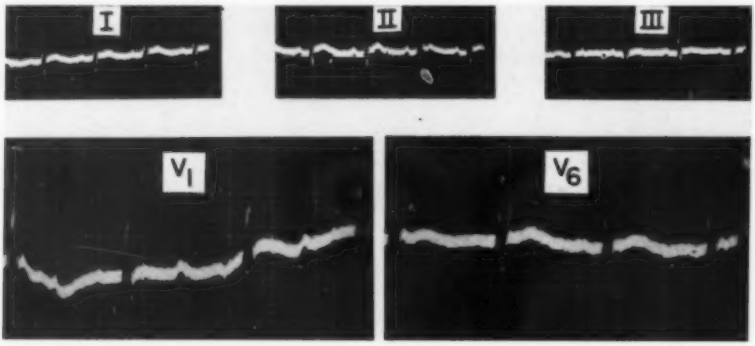


Fig. 3A.—Case 3. Electrocardiogram before treatment, at the age of 3 months. Intrinsicoid deflection in V_1 is at 0.038 second; note right axis deviation.

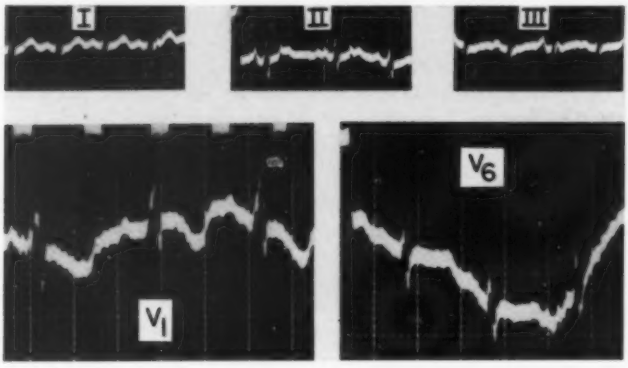


Fig. 3B.—Case 3. Electrocardiogram of patient at the age of 2½ years, after thyroid therapy for more than 2 years. The amplitude of R in V_1 has diminished moderately, there is less right axis deviation, but the delayed intrinsicoid deflection in V_1 has not improved. Clinically, the patient had improved and was growing well.

in all of them there are an abnormally broad S wave and wide QRS in Lead I, presuming that the electrodes for the left and right arms are reversed in "Kurve 4," as they appear to be. Other studies[23, 24] have also shown a broad slurred S wave in Lead I of untreated adult patients with myxedema, but only the changes in QRS and T voltage with therapy have been reported, with rare comment on the contour of QRS.

only one, a woman of 53 years who had atherosclerotic heart disease, had an R′ wave in either V_1 or aV_R. This group included both postirradiation (I^{131}) and postthyroidectomy myxedema patients as well as those with primary hypothyroidism. This may account for some electrocardiographic differences, for it has been our experience that patients with primary myxedema are more likely to show the classical low QRS and T voltage, for

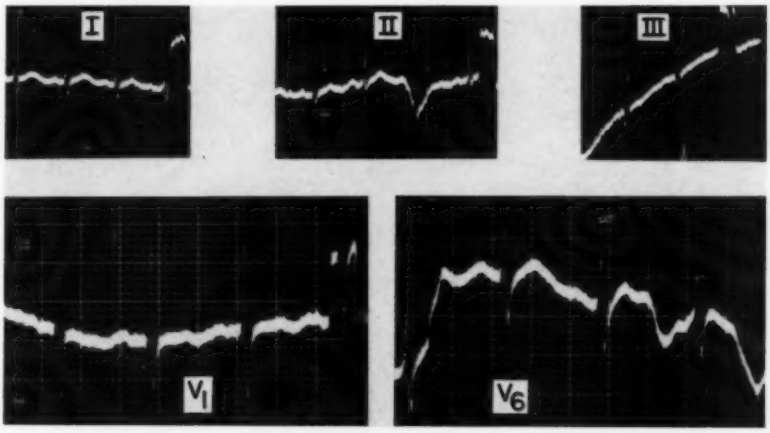


Fig. 4.—Case 4. Electrocardiogram before treatment, at the age of 30 months. Amplitudes of R and S in V_1 are 11 and 7 mm., respectively; the intrinsicoid deflection in V_1 is 0.02 second. The ratio of R to S in V_1 exceeds the normal range for this age group.[8] No subsequent tracings were obtained.

Lack of previous recognition of right bundle branch block in adult patients with myxedema may be due to the fact that most studies on the electrocardiogram in myxedema were made before the widespread use of precordial leads. In a brief review of the last 25 cases of adults with the diagnosis of myxedema at the Ochsner Clinic, 12 had electrocardiograms just before institution of therapy. In 7 of these, the contour and duration of QRS were normal. In 5 there was minor slurring of the S wave in Leads I and V_6 but

example, than patients with secondary myxedema. If the observation of delayed right ventricular excitation in the electrocardiogram of adult patients with untreated myxedema is correct (it should be investigated by additional observers) it may be unreasonable to postulate a different mechanism in the infant with cretinism.

In the untreated infant with cretinism delayed activation of the right ventricle probably represents, at least partly, persistence of the fetal or neonatal state of the heart which has

failed to evolve from right toward left ventricular preponderance in the normal fashion. This is consistent with the delay in development characteristic of other body systems of the cretin, notably of the cerebral and skeletal systems. A lack of thyroid hormone, of growth hormone,[25] or of both may be responsible for this generalized retardation. The less impressive right ventricular delay in the electrocardiogram of Case 4 (aged 30 months) may mean that the cretin heart eventually develops to some extent even without thyroid therapy.

Unfortunately, the theory of delay in normal evolution of the heart, which might explain the preponderant right ventricular voltage, does not adequately explain the actual delay in right ventricular excitation apparent in most of our cases. In the absence

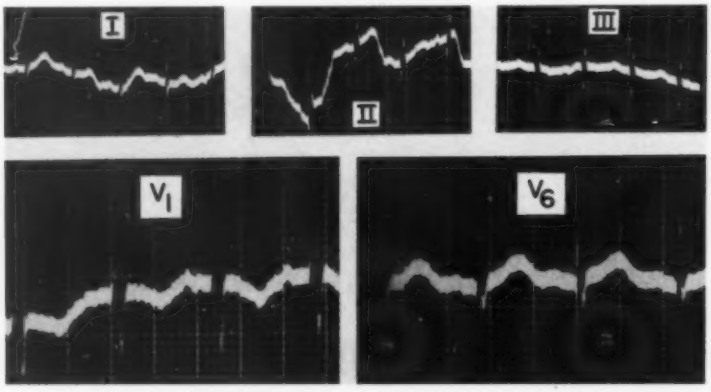


Fig. 5*A*.—Case 5. Electrocardiogram at age 13 months, before treatment. Intrinsicoid deflection in V_1 is 0.028 second, amplitudes of R and S are 12 and 7 mm., respectively. The large Q wave in II and III has been commented on by others.[6]

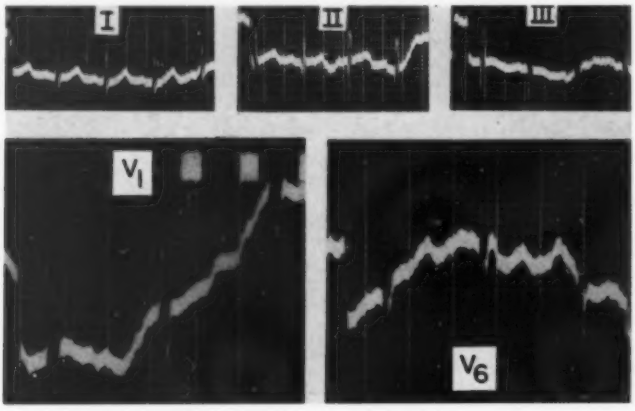


Fig. 5*B*.—Case 5. Electrocardiogram after only 12 days of treatment with thyroid. Amplitude of R in V_1 has diminished and in V_6 increased; patient was definitely more alert; alkaline phosphatase during the same period had increased from 3.8 to 8.7 Bodansky units.

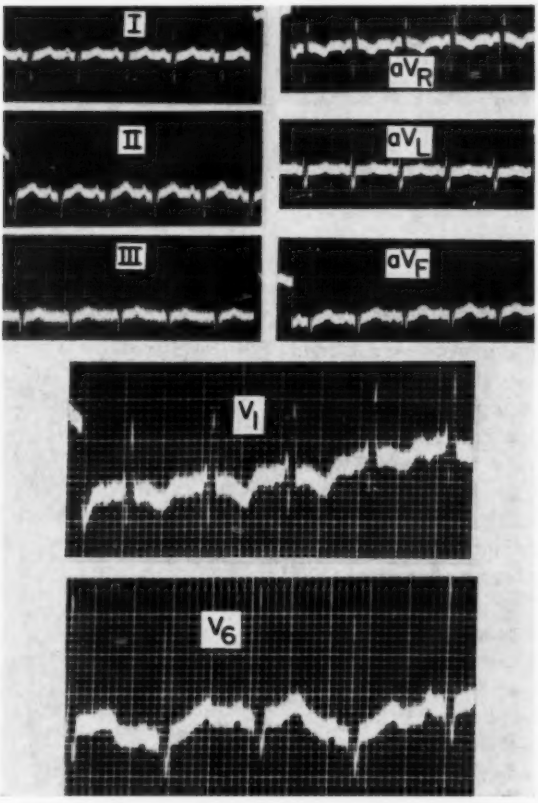
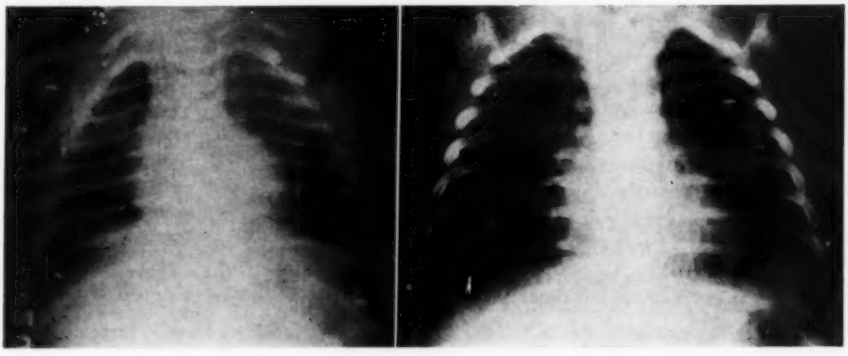


Fig. 6.—Case 6. Electrocardiogram at the age of 5 months, after inadequate doses of thyroid extract had been given for 2 months. The height of R′ in V_1 with QRS duration of only 0.08 second suggests this is not a conventional right bundle branch block but might represent right ventricular hypertrophy. No subsequent tracings were available.



A. *B.*

Fig. 7.—*A*, Case 1. Roentgenogram at the age of 3 months, before treatment. *B*, Case 6 at the age of 5 months, after 2 months of inadequate treatment.

of right ventricular hypertrophy, this delay is probably due to a lesion involving the right bundle branch. A focal lesion is more likely to manifest itself electrocardiographically in the right bundle branch, which leaves the bundle of His as a single bundle, than in the left bundle branch, which early divides into a number of separate bundles.[26, 27]

Focal lesions in the heart are not generally considered characteristic of myxedema per se, except as a secondary manifestation of atherosclerosis in adults.[26] One exception is Monaci and Weber's[29] postmortem study of the cardiac conduction system of a cretin at 4 months of age in whom degenerative changes in the A-V bundle and neighboring conduction tissue were observed. Diffuse nonspecific myocardial changes consisting of hydropic degeneration and interstitial edema have been more frequently described, similar to changes produced by myxedema throughout the body.[10, 26, 28] Since these are diffuse changes, however, it is difficult to understand why the right bundle branch should be preferentially involved even though it is a single trunk. Nevertheless, it must be noted that 2 of our 7 patients had right bundle branch block.

One other consideration that may be a factor is the possibility that left ventricular metabolism suffers more than that of the right ventricle in myxedema, with diminution in its electrical voltage, consequently increasing relatively the apparent voltage from the right ventricle.

Whatever its explanation, delayed right ventricular excitation in the electrocardiogram of infants with untreated cretinism seems characteristic of that state. Both this observation in the untreated child and the question of its reversibility should be examined by others, for it may prove to be a valuable diagnostic addition in suspected cretinism. Conversely, the diagnosis of cretinism should perhaps be considered more frequently in infants with unexplained "right ventricular hypertrophy" on their electrocardiograms.

SUMMARY

Delayed excitation of the right ventricle was found in the electrocardiograms in 5 of 7 untreated cretins. Possible explanations for this observation are discussed. The most logical probabilities are a delay in normal evolution of the newborn infant's heart and a focal lesion involving the right bundle branch, or both.

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SEASONAL DISTRIBUTION OF INITIAL APPEARANCE OF POSTNATAL OSSIFICATION CENTERS IN HAND AND WRIST OF UNDERNOURISHED CHILDREN

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HUMAN physical growth is characterized by fluctuations in rate which, in part, follow a seasonal pattern.[1, 2] Most studies contribute to the inference of a periodicity in height and weight gain with the greatest increase in weight occurring in the autumn and the maximum gain in height occurring in the spring.[3] The periods of greatest height gain are thus counterbalanced by periods of least weight gain and vice versa. In addition to influencing dimensional growth as reflected by height and weight, season apparently affects skeletal development. In healthy children, Reynolds and Sontag[4] found that the maximum rate of appearance of selected centers of ossification extends from March to May and the minimum from September to November. Bransby[5] maintains, however, that seasonal variations in growth rate are not natural and proper phenomena and that they should be interpreted as signs of less than optimum growth rate.

Protracted undernutrition during the growth period seemingly alters the seasonal growth pattern. As previously reported from this Clinic, the incidence of retarded growth in white Alabama children with chronic nutritive failure is greatest in June through August.[6] These findings were derived from analyses of the Wetzel Grid curves in which height and weight were treated as a single function. The time of the year during which episodes of retarded growth were most frequent coincided with that during which the lesions of nutritional deficiency diseases in this group became manifest. Recently, it was shown that chronic undernutrition delays the time of appearance of the postnatal ossification centers in the hand and wrist.[7] These studies have now been extended to determine whether nutritive failure exerts a seasonal influence on the initiation of mineralization in the postnatal ossification centers.

MATERIALS AND METHODS

Serial roentgenograms of the left hand and wrist of 282 children in the growth study series of the Nutrition Clinic, Hillman Hospital, Birmingham,

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Alabama, were examined and the date of appearance of 31 postnatal ossification centers determined by extrapolation to the nearest month. Only those centers in which roentgenographic evidence of onset of ossification could be accurately detected were included. The chronologic age at which each center was first noted was contrasted with the standards contained in the Greulich-Pyle Atlas.[8] The roentgenograms used in this study had been taken every 3 months until the child was 5 years of age and every 6 months thereafter. Each child selected had clinical and laboratory evidence of chronic nutritive and growth failure based on previously reported diagnostic criteria.[9] The 282 children, 157 boys and 125 girls, ranged in age from 3 months to 13 years, 6 months. Each was white, of British extraction, and a native of north central Alabama.

The seasonal distribution of the time of appearance of the ossification centers in the hand and wrist was evaluated in terms of sex, month of birth, and type of center. The data were then subjected to statistical analysis.

OBSERVATIONS

The month of appearance was identified for 5,043 postnatal ossification centers of which 1,172 were primary (carpals and thumb sesamoids) and 3,871 were secondary (metacarpal and phalangeal epiphyses and distal epiphysis of the radius and ulna). The mean time of appearance for each of the 31 ossification centers in the hand and wrist was delayed in every instance in each sex. The lag in advent of ossification was much more pronounced in the carpals than in the metacarpal and phalangeal epiphyses. In both sexes the delay in the emergence of the epiphysis of the distal ulna greatly exceeded that of the distal epiphysis of the radius. Quantitatively, the mean retardation in appearance of the primary centers was 14.83 months (boys) and 11.95 months (girls) and of the secondary centers, 11.38 months (boys) and 5.64 months (girls).

The seasonal distribution of the time of appearance of the postnatal ossification centers in the hand skeleton of the 282 children is shown in Figure 1. Regardless of type, the greatest number of centers began to ossify in the summer (total, 30.9 per cent; primary, 28.8 per cent; secondary, 31.4 per cent). The smallest number appeared in the winter (total, 19.2 per cent; primary, 23.3 per cent; secondary, 18.1 per cent). The months in which the largest number of primary, secondary, and total centers were first visible roentgenographically were August, March, and August, respectively. The differences between the number of primary, secondary, and total centers appearing in the summer and in each of the other seasons were statistically significant. The actual difference in per cent between the number of primary and secondary centers combined which first emerged in the summer in contrast to the winter, spring, and autumn exceeded the standard error of difference between proportions ($\sigma_{D\%}$) by 13.9, 5.6, and 7.7 times, respectively. The corresponding ratios for the primary centers were 3.5, 3.1, and 2.6 and for the secondary centers, 13.7, 6.8, and 7.1. An actual difference in per cent 2 or more times the standard error of difference between proportions is indicative of statistical significance.[10]

A similar seasonal distribution obtained when the appearance of centers

TABLE I. SEXUAL DISTRIBUTION OF SEASON OF APPEARANCE OF POSTNATAL OSSIFICATION CENTERS IN HAND AND WRIST OF 282 UNDERNOURISHED CHILDREN

SEASON	PRIMARY CENTERS						SECONDARY CENTERS						TOTAL CENTERS					
	BOYS		GIRLS		TOTAL		BOYS		GIRLS		TOTAL		BOYS		GIRLS		TOTAL	
	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%
Winter	137	22.9	136	23.7	273	23.3	401	18.5	298	17.4	699	18.1	538	19.5	434	19.0	972	19.2
Spring	147	24.6	133	23.2	280	23.9	560	25.9	463	27.1	1,023	26.4	707	25.6	596	26.1	1,303	25.9
Summer	165	27.6	173	30.1	338	28.8	676	31.2	539	31.6	1,215	31.4	841	32.8	712	31.2	1,553	30.9
Fall	149	24.9	132	23.0	281	24.0	526	24.3	408	23.9	934	24.1	675	24.4	540	23.2	1,215	24.1
Total	598		574		1,172		2,163		1,708		3,871		2,761		2,282		5,043	

was grouped according to sex (Table I). Of the 2,761 centers in the boys, 841 (32.8 per cent) appeared in the summer; of the 2,282 centers in the girls, 712 (31.2 per cent) appeared in the same period. The least number of centers emerged in the winter, 538 (19.5 per cent) in the boys and 434 (19.0 per cent) in the girls. The variation in season of appearance of the secondary centers was the same as for the summer in contradistinction to those which became manifest in the winter, spring, and autumn were statistically significant. In the boys the ratios of actual difference in per cent to the standard error of difference between proportions were: summer versus winter, 11.4, summer versus spring, 5.9, and summer versus autumn, 6.9. For the girls, the corresponding ratios were 9.6, 3.8, and 6.1.

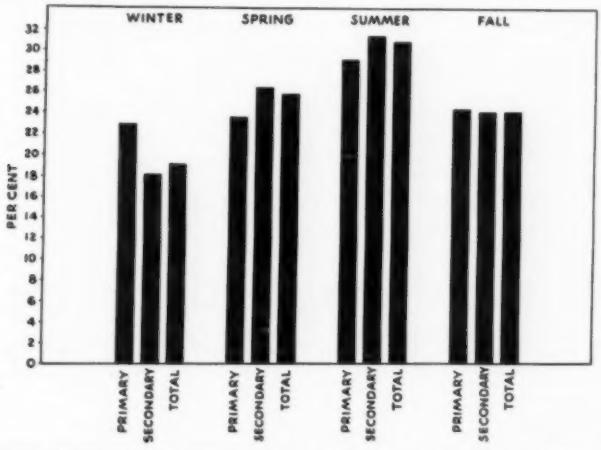

Fig. 1.—Seasonal distribution of appearance of postnatal ossification centers in hands of 282 undernourished children.

the total centers with highs in the summer of 31.2 per cent for the boys and 31.6 per cent for the girls, and lows in the winter of 18.5 per cent for the boys and 17.4 per cent for the girls. Regardless of sex, more centers appeared in August than in any other month. Whereas most of the primary centers emerged in the summer in both boys (27.6 per cent) and girls (30.1 per cent), the lowest number of primary centers appeared in winter in the boys (22.9 per cent) and in autumn in the girls (23.0 per cent).

For each sex, the differences between the number of primary and secondary centers combined which appeared in

In both the boys and girls the number of primary centers which appeared in the summer was significantly greater than the number presenting in the winter, with ratios of 2.1 for the boys and 2.7 for the girls. In the girls, the number of primary centers which emerged in the summer exceeded those first visualized in the spring and fall to a significant degree, the respective ratios being 3.2 and 2.6. In the boys the difference between the numbers appearing in the summer and those appearing in the spring and fall were not statistically significant (summer versus spring, 1.1, and summer versus fall, 1.0). The differences between the

number of secondary centers which began to ossify in the summer and those which appeared in each of the other seasons were significant in both sexes: summer versus winter, 9.8 (boys) and 9.9 (girls); summer versus spring, 3.9 (boys) and 2.9 (girls); summer versus fall, 5.1 (boys) and 5.0 (girls).

present findings show that chronic undernutrition not only retards the emergence of the ossification centers, but also alters the characteristic seasonal pattern associated with their appearance. In the present series the peak of appearance of ossification centers in June through August was approximately 3 months later than that

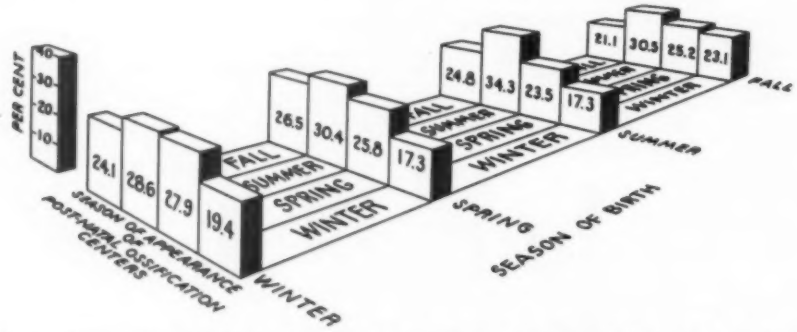

Fig. 2.—Comparative distribution between season of birth and season of appearance of postnatal ossification centers in hands and wrists of 282 undernourished children.

As shown in Fig. 2, the season of appearance of the 31 postnatal ossification centers in the hand and wrist of the 282 undernourished children bore no relationship to the season of birth. Irrespective of season of birth, the greatest number of centers appeared in the summer and the least in the winter.

DISCUSSION

Although the precise mechanism which precipitates the conversion of the cartilaginous primordium into osseous tissue is unknown, studies in this clinic indicate that it is influenced to a detectable degree by nutritional status. Illustrative of this influence is the recent demonstration of a pronounced delay in the initiation of mineralization in the postnatal ossification centers of the hand skeleton in children with chronic nutritive failure.[7] The

noted by Reynolds and Sontag[4] for adequately nourished children in southwestern Ohio.

The time of most frequent appearance of the ossification centers in the undernourished children coincided with the period during which such children show the highest incidence of retarded growth on the Wetzel Grid.[6] The dichotomy can best be resolved in terms of the hypothesis advanced by Sargent and Sargent[11] concerning the role of seasonal variations in human biochemical processes and functional mechanisms. The seasonal cycle is regarded as essentially a nutritional cycle modified by environmental stimuli such as sunlight and temperature. In their evaluation of the temporal aspects of the relationship between nutritional deficiency states and

food intake in the southeastern United States, Sargent and Sargent[11] concluded that there is a seasonal variation in tissue demands for essential nutrients. From April to September there is an increased need for protein and water-soluble vitamins and from October to March there is an elevated metabolic requirement for fat and fat-soluble vitamins. The nutrient value of the home diets consumed by children with nutritive failure in the Nutrition Clinic series shows a distinct seasonal variation.[12] The intake of protein, thiamin, riboflavin, niacin, and iron is greatest during the winter and least in summer; that of calcium, phosphorus, and vitamins A, C, and D is highest in the late spring and summer and lowest in the fall and winter. The high incidence of retardation in general body growth during June through August in children with chronic undernutrition may thus be attributable to a failure to meet the increased tissue requirements for protein and water-soluble vitamins during this period. Conversely, the ability of the undernourished children to meet the diminished demands for fat-soluble vitamins during the spring and summer may account for the peak of appearance of the ossification centers in the period extending from June through August.

SUMMARY AND CONCLUSIONS

The time of appearance of 31 postnatal ossification centers in roentgenograms of the hand and wrist of 282 undernourished children has been shown to follow a seasonal pattern which is not related directly to sex, type of center, or month of birth. The number of centers initially appearing in the summer (31 per cent) was greater to a statistically significant degree than that emerging in any other season. The temporal coincidence of a peak in occurrence of new ossification centers and a diminution in rate of general body growth may be related to a seasonal variation in the availability and utilization of specific nutrients and accessory food factors.

We wish to acknowledge the technical assistance of Mrs. Hamilton Webb-Peploe.

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KANAMYCIN* IN URINARY TRACT INFECTIONS IN CHILDHOOD

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KANAMYCIN, recently discovered by Umezawa and associates,[1, 2] is an antibiotic elaborated by *Streptomyces kanamyceticus*.[1, 2] It is chemically related to neomycin and streptomycin.[3] Its antibacterial spectrum includes both gram-positive and gram-negative organisms and resembles closely that of neomycin.[4]

Kanamycin is poorly absorbed when administered orally. However, it can be effectively administered for systemic use by intramuscular injection.[5, 6] There is minimal binding of kanamycin to serum proteins,[4] and most of the drug administered intramuscularly is excreted in the urine by glomerular filtration within 24 hours.[7]

Kanamycin has been found to be of value in staphylococcal infections and in systemic infections caused by susceptible gram-negative organisms.[6, 8] It has been reported to be effective in the control of urinary tract infections in adults.[9-11] There have been a few scattered reports of cases of urinary tract infections in childhood treated with this drug.[8, 12]

Since kanamycin may have significant ototoxic and nephrotoxic effects,[6, 12, 13] it is important to define clearly the value and limitations of the drug in pediatric practice. It is the purpose of this paper to report a study of the effect of kanamycin in urinary tract infections in children.

MATERIAL AND METHODS

Twenty children with urinary tract infection were included in the study. They ranged in age from 3 months to 13 years. The criterion for establishing the presence of urinary infection was the observation of more than 5 leukocytes per high-power field in the urine sediment and the recovery of more than 10^5 colonies of bacteria per milliliter of urine. Urinary tract infections were classified as either acute or chronic according to the duration of symptoms prior to therapy.

Quantitative urine cultures were made immediately prior to kanamycin therapy, on the last day of therapy, and one week after therapy had been discontinued. Catheterized samples were obtained from females and clean voided midstream samples from males. Urinalysis was done on each specimen cultured. A 10.0 ml. aliquot of the specimen was centrifuged at 2,000 r.p.m. for 5 minutes, and the sediment was examined for cellular elements. Bacteria recovered from the urine were tested for sensitivity to kanamycin by a tube dilution method, using antibiotic assay broth.* All strains recovered were also tested for sensitivity to other

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*Kanamycin was supplied as Kantrex by the Bristol Laboratories Inc.

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antibiotics by a paper disc method employing Difco heart infusion agar medium and Difco antibiotic discs.

An intravenous pyelogram was done on each patient. The concentration of nonprotein nitrogen in the blood was also determined on each patient prior to and one week after therapy. Additional studies were done as indicated.

Each patient was treated in the hospital with kanamycin which was administered in a dosage of 20 mg. per kilogram per day. The drug was given every 6 hours to patients whose admission numbers were odd and every 12 hours to patients whose numbers were even. Treatment was continued for a period of 7 days except in one case in which an allergic reaction necessitated earlier withdrawal of the drug. The children have been followed clinically for periods of one month to 8 months after kanamycin therapy.

Kanamycin levels were determined on serum samples obtained 1 hour, 2 hours, and 5 hours after the institution of kanamycin therapy in patients on both schedules. In addition a 10 hour sample was obtained from patients on the 12 hour schedule. Kanamycin assays* were also made on urine collected for the first 24 hours after the institution of therapy. Streptomycin assay agar with yeast extract† was used for both the base and the seed agar. *Bacillus subtilis* A.T.C.C. 6633 was used as the test organism.

RESULTS

Prior to therapy, 13 strains of *Escherichia coli*, 10 Proteus, 4 Paracolon, 3 Aerobacter, 10 Enterococcus, and 1 coagulase-positive Staphylococcus were recovered (Table I). In several cases more than one strain of bacteria were recovered. The in vitro sensitivities of these bacteria to kanamycin are also included. The range of sensitivity was wide. In general, it can be noted that 11 of the strains of *E. coli* were inhibited by 62 mcg. per milliliter of kanamycin, and that 8 of the strains of Enterococcus were resistant to the same concentration.

Results in each case were evaluated in terms of response of symptoms, clearing of the urinary sediment, and eradication of infecting bacteria. The response to kanamycin may be seen in

TABLE I. CULTURES PRIOR TO THERAPY

ORGANISMS	SENSITIVITIES TO KANAMYCIN*						TOTAL
	S8	S16	S31	S62	S125	R125†	
Gram-Negative.—							
E. coli	–	–	9	2	1	1	13
Proteus species	–	–	1	6	3	–	10
Paracolon species	1	–	2	1	–	–	4
Aerobacter species	2	–	1	–	–	–	3
							30
Gram-Positive.—							
Enterococcus	–	–	1	1	2	6	10
Micrococcus, coagulase positive	–	–	–	–	–	1	1
							11

*Minimal inhibiting concentration expressed in mcg./ml.
† S = sensitive; R = resistant.

*The kanamycin assays were performed by an agar plate method through the courtesy of Bristol Laboratories Inc.

†Baltimore Biological Laboratory No. 01-266.

TABLE II. CLINICAL EFFECT OF KANAMYCIN (WITHIN 1 WEEK'S FOLLOW-UP)

URINARY TRACT INFECTIONS	NUMBER OF PATIENTS	RESPONSE OF SYMPTOMS AND SIGNS		RESPONSE OF URINARY SEDIMENT		BACTERIOLOGIC RESPONSE	
		GOOD	POOR	GOOD	POOR	GOOD	POOR
Acute	13	12	1	12	1	10	3
Chronic	7	5	2	4	3	4	3
Total	20	17	3	16	4	14	6
Percentage		85		80		70	

TABLE III. ANTIBACTERIAL EFFECT OF KANAMYCIN (BEFORE AND ON THE SEVENTH DAY OF THERAPY)

ORGANISMS	TOTAL NUMBER BEFORE THERAPY	ERADICATED	SUPPRESED	PERSISTING	EMERGENT	TOTAL
Gram-Negative.—						
E. coli	13	11	1	–	1	13
Proteus species	10	10	–	–	1	11
Paracolon species	4	3	1	–	–	4
Aerobacter	3	3	–	–	–	3
Pseudomonas	—	—	–	–	1	1
	30	27				
Gram-Positive.—						
Enterococcus	10	8	1	1	–	10
Micrococcus, coagulase positive	1	1	–	–	–	1
	11	9				

Table II. It will be noted that in the acute urinary tract infections, 12 of 13 cases showed good symptomatic response with disappearance of fever, urinary frequency, and localized tenderness. Urinary sediment in these cases returned to normal, and pus cells were no longer found. Bacteria were no longer recovered in a concentration of greater than 10^3 colonies per milliliter from the urine of 10 of the 13 patients with acute cases. As expected, the response in chronic urinary tract infection was less satisfactory. Good symptomatic response was obtained in 5 of 7 cases. In one of these cases, however, the symptomatic response was short-lived. Clearing of the urine sediment and eradication of bacteria resulted in 4 of 7 cases. It will be noted that of the total group of 20 patients, 85 per cent showed good symptomatic response, 80 per cent showed clearing of the urine sediment, and 70 per cent showed an excellent bacteriologic response to kanamycin therapy.

The effect of kanamycin therapy on the urinary bacteria by the seventh day of therapy is summarized in Table III. Twenty-seven of the 30 gram-negative organisms and 9 of the 11 gram-positive organisms were eradicated. All of the original Proteus and Aerobacter strains were eradicated. One strain each of *E. coli*, Paracolon, and Enterococcus was suppressed and one strain of Enterococcus persisted. One strain each of *E. coli*, Proteus, and Pseudomonas emerged during therapy.

The bacteriologic status of the urine one week after cessation of therapy is shown in Table IV. It may be noted that 6 gram-negative and 3 gram-positive strains were recovered. Both strains of persisting Enterococcus and all the emergent strains of Proteus and

Pseudomonas were resistant in vitro to 62 mcg. per milliliter of kanamycin. On the other hand, one persisting strain of coagulase-positive Staphylococcus and one of *E. coli* were inhibited in vitro by 16 mcg. per milliliter of kanamycin; one emergent *E. coli* strain and one persisting Paracolon strain were inhibited by 62 mcg. per milliliter. Moreover, several strains of bacteria which showed relative in vitro resistance to kanamycin were eradicated. Paper disc sensitivities to other antibiotics revealed but one strain of *E. coli* which had a different sensitivity as compared to the pretreatment culture.

Table IV. Cultures One Week After Cessation of Therapy

Organisms	Sensitivities to Kanamycin*						Total
	S8	S16	S31	S62	S125	R125†	
Gram-Negative.—							
E. coli	–	1	–	1	–	–	2
Pseudomonas	–	–	–	–	1	1	2
Paracolon species	–	–	–	1	–	–	1
Proteus species	–	–	–	–	–	1	1
							6
Gram-Positive.—							
Enterococcus	–	–	–	–	–	2	2
Micrococcus, coagulase positive	–	1	–	–	–	–	1
							3

*Minimal inhibiting concentration expressed in mcg./ml.
†S = sensitive; R = resistant.

Table V. Successfully Treated Cases Despite Predisposing Causes for Infection

Patients	Predisposing Factors	Type of Infection
D. R.	Bilateral hydronephrosis	Acute
L. W.	Acute balanitis and phimosis	Acute
B. J. H.	Indwelling urethral catheter	Acute
M. M.	Bifid right kidney and double ureter	Chronic
H. J. F.	Hydronephrosis of upper pole of right kidney Neurogenic bladder and ureter Bilateral hydronephrosis and hydroureter	Chronic
J. L.	Hydronephrotic cyst of upper pole of right kidney	Chronic

Despite predisposing causes for infection, 6 cases responded well to therapy (Table V). In 2 of these patients, operative procedures were performed at the conclusion of therapy. In H. J. F., a ureteronephrectomy was performed on the more involved left side. This patient had been on many different antibiotics prior to therapy. After 7 days of kanamycin therapy, the symptoms were ameliorated, the urine sediment was clear, and the culture was sterile. Following the operative procedure, no antibiotics were given. He has remained asymptomatic for the past 7 months, and urine cultures have remained negative. In patient J. L., it was believed that a hydronephrotic cyst of the upper pole of the right kidney was responsible for the chronic urinary tract infection. After kanamycin therapy, a right ureterohemineprectomy was performed. This patient has been followed for two months. She is asymptomatic, and urine cultures are negative. In patient L. W., who had acute balanitis and phimosis,

a circumcision was performed after therapy. In B. J. H., the indwelling catheter was removed at the end of treatment.

On the other hand, several patients with predisposing urinary tract disease were not relieved of their infection by kanamycin therapy. In Table VI it will be noted that included in this group are: one patient with cystitis cystica,[14] one with nephrocalcinosis,[15] and 2 with hydronephrosis and congenital anomalies of the kidney and ureter[16] severe enough to necessitate indwelling suprapubic cystostomy tubes. Of these 4 patients, 2 had a temporary response to therapy. A recurrent infection with the same organism occurred in one patient, however, and reinfection with a new organism, a Pseudomonas, occurred in the other. One patient who failed to show a temporary response had low levels of kanamycin in the serum and urine. In J. M., therapy was discontinued after 2 days because of an urticarial rash presumably caused by an allergy to kanamycin. Three patients with no evident underlying urinary tract disease were not relieved of infection by kanamycin therapy. In the case of R. T., the patient was relieved of infection with *E. coli* but one month later was found to have an *Aerobacter aerogenes* infection. Two brothers, G. S. and K. S., both suffering from a familial form of hepatitis, were not permanently relieved of urinary tract infection by kanamycin despite no apparent underlying predisposing urinary tract disease. G. S. was treated for *E. coli* septicemia and pyelonephritis. He recovered from the septicemia, and his urine was temporarily sterile, but he was found to have a recurrent *E. coli* urinary tract infection a week after the end of therapy. This was believed to be a new strain of *E. coli* because its sensitivity to tetracycline and chloramphenicol as well as to kanamycin differed from the sensitivities to these antibiotics of the *E. coli* strain originally recovered. K. S. also showed only a temporary response to therapy.

TABLE VI. CASES OF PERSISTENT INFECTION DESPITE KANAMYCIN THERAPY

PATIENTS	APPARENT CAUSES	TEMPORARY RESPONSE	TYPE OF INFECTION
R. T.	Reinfection with another organism	Yes	Acute
G. S.	None apparent	Yes	Acute
K. S.	None apparent	Yes	Acute
K. B.	Cystitis cystica Low serum kanamycin level	Yes	Chronic
R. P.	Nephrocalcinosis secondary to idiopathic hypercalcemia	Yes	Chronic
M. H.	Bilateral hydronephrosis and hydroureter Indwelling suprapubic cystostomy tube Low kanamycin levels in serum and urine Emergent organism	Equivocal	Chronic
J. M.	Bilateral bifid kidney and double ureter Left hydronephrosis and hydroureter Indwelling suprapubic cystostomy tube Emergent organism Inadequate therapy due to allergic reaction	No	Chronic

Kanamycin Assays.—Serum kanamycin levels were determined in 13 patients on the 6 hour regimen. The mean values for 1 hour, 2 hours, and 5 hours were 10.2 meg., 9.4 meg., and 2.6. meg. per milliliter, respectively. Standard deviations were ± 4.8 meg. per milliliter in the 1 hour group, ± 5.3 meg. per milliliter in the 2 hour group, and ± 3.5 meg. per milliliter in the 5 hour group. The patients on the 12 hour regimen had serum levels determined at 1 hour, 2 hours, 5 hours, and 10 hours. This group was composed of 4 patients. Mean values were 27.2 meg. per milliliter at 1 hour, 15 meg. at 2 hours, 5.8 meg. at 5 hours, and 0.4 meg. at 10 hours. Standard deviations were not calculated because of the small number of patients in this group.

Kanamycin levels were determined on 24 hour urine collections in 11 patients. The mean concentration of kanamycin was 390 meg. per milliliter with a standard deviation ± 232 meg. When these values were expressed as the percentage excreted of the total 24 hour dosage administered, the mean value was 68 per cent excretion in 24 hours. The results of these assays are in general agreement with those reported by Berger, and Wehrle,[5] Bunn,[6] and High[8] and their co-workers.

DISCUSSION

A short course of kanamycin therapy appears to be effective in many urinary tract infections in childhood. Infections may respond even when serum levels of kanamycin achieved are below the minimum concentration necessary to inhibit the infecting organism in vitro. This may be due to the high levels of kanamycin which are obtained in the urine, and possibly also to the bactericidal properties of the antibiotic.

Kanamycin has been shown to be effective in some cases when predisposing causes are present. Best results are obtained when the urinary tract abnormalities are corrected following the kanamycin therapy.

Failures are to be expected in the face of infection with organisms resistant to kanamycin, or infections with severe noncorrectible predisposing urinary tract disease. Even with sensitive organisms and no associated urinary tract anomaly, occasional failures may be seen. New strains or species of organisms which are generally resistant to kanamycin may emerge during therapy.

Since kanamycin has potentially significant ototoxic and nephrotoxic effects, it is important that the use of the drug in urinary tract infections in children be limited to carefully selected cases. No significant toxicity to kanamycin was found in this study. Since it was not feasible to perform audiometric tests on these patients, however, it is possible that impairment of hearing induced by kanamycin may have gone undetected. When higher doses of kanamycin and longer therapy are employed, a greater incidence of toxicity is to be expected.[6, 13] In the presence of azotemia, high serum levels may be anticipated since the drug is excreted primarily by the kidneys. Therefore, the standard regimen used in this study is not recommended as a routine in cases with severe impairment of renal function.

Thurman and Platou[12] have recommended that the interval between doses should be no less than 8 hours and

preferably 6 hours. In their study an earlier clinical and temperature response was obtained on the 6 hour schedule as opposed to the 12 hour schedule. While it should be noted that the number of patients in our study was limited, it appeared that the patients on the 6 hour and 12 hour schedules had similar clinical and bacteriologic responses.

Kanamycin has some obvious disadvantages. The need for intramuscular administration makes it difficult to use on an outpatient basis. While no local reactions were observed, intramuscular injections in general are not employed in children when oral medication can achieve similar results. Thus, the older therapeutic agents which may be administered orally are still the preferred medications in the initial treatment of most urinary tract infections in childhood.[16, 17] Therapy with kanamycin should be considered in infections which have failed to respond to the older medications such as tetracycline and chloramphenicol. The in vitro sensitivity of the bacteria isolated may on occasion indicate the use of kanamycin as the initial medication. In patients with infections of great severity who have had previous courses of other antibiotics, and particularly in instances where oral medication is not tolerated, the use of kanamycin should be considered.

Kanamycin appears to be an effective antibiotic in most Aerobacter and *E. coli* infections. Proteus infections which usually fail to respond to any of the older antibiotics will frequently respond to kanamycin. Some Enterococcus infections also respond to kanamycin. Although no Pseudomonas infections were treated in this study, the relative in vitro resistance of this organism to kanamycin indicates that this type of infection would seldom be eradicated. Kanamycin appears to be valuable in some infections caused by organisms resistant to other antibiotics and in some patients with correctible urinary tract anomalies. When prolonged therapy is needed, kanamycin is not indicated because of its potential toxic effects and the need for parenteral administration.

Kanamycin appears to be another useful drug in the treatment of urinary tract infections in childhood. Because of potential toxic effects, limited antibacterial spectrum, and the need for parenteral administration, kanamycin should not be used indiscriminately. Careful evaluation of each patient, including indicated urologic and bacteriologic evaluation, is an essential prerequisite to obtaining optimal results with kanamycin in urinary tract infections.

SUMMARY

Kanamycin was used to treat 20 cases of acute and chronic urinary tract infections in childhood. The drug was administered intramuscularly for 7 days in a dosage of 20 mg. per kilogram per day.

Kanamycin was effective in a large percentage of these infections. Patients with acute infections and correctible urinary tract anomalies responded better than those with chronic infections and noncorrectible anomalies.

Kanamycin appears to be another effective antibiotic for urinary tract infections in childhood. The potential ototoxic and nephrotoxic effects of the drug should be borne in mind when its use is considered.

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EXCRETORY UROGRAPHY IN INFANTS AND CHILDREN

Improved Results Through the Use of Postero-oblique Projections

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EXCRETORY urography in infants has always presented technical difficulties because of the virtual impossibility of avoiding gas accumulation in the intestines.[1-6]

To overcome these obstacles various methods of preparing the patient have been suggested,[6, 7] but "elaborate preliminary dietary and eliminant measures to reduce intestinal gas prior to the examination are usually ineffective,"[1] and "even today roentgenologists disagree on methods for eliminating the intestinal gas, and certainly the child should be spared purging enemas 'until the return is clear,' and starvation."[4]

Two ways by which one may try to obtain a satisfactory examination are: (a) elimination of gas, and (b) evasion of gas.

Of these, attempts at elimination have proved erratic, while attempts to evade the gas by improvements of the examination have more often produced satisfactory results.

In efforts to evade intestinal gas, we distinguish between two different principles—improvement of (1) mechanical procedures, and (2) radiographic procedures.

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Improvement of Mechanical Procedures

The object of the methods based on this principle is the displacement of the gas-filled intestinal loops by the distended stomach, and it is achieved by filling the stomach either with fluid or with gas and fluid.[2, 5, 8]

A combination of both gas and fluid is achieved by administration of soda water, sweetened with saccharine, which distends the stomach and thereby presses the intestines down into the distal half of the abdomen so that the pyelographic shadows are visualized.[5]

The artificial distention of the stomach by fluid was discovered by Matthei,[2] when he noticed that, in a baby who was given his formula by mistake immediately before the examination, the distended stomach displaced the bowels and offered an unobstructed view of the kidney regions.

In either method the examination is started by injection of the contrast medium, following which the feeding is begun. If the feeding is given before the injection, part of the fluid will have left the stomach before pictures can be taken, and the desired result may not be achieved.

In order to increase the eagerness for the feeding, the infant is kept without fluids for 12 hours prior to the examination. This is done not

only because it enhances the concentration of dye in the pyelographic picture, but especially because slow drinking may delay the filling of the stomach until excretion of the contrast medium, and are in poor general condition, a period of 12 hours of dehydration may cause deterioration. Moreover, it is certainly not possible to keep these infants without fluids during the long

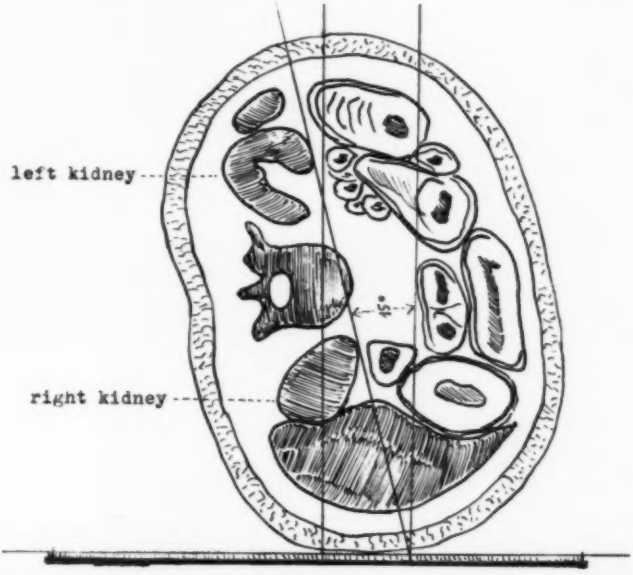
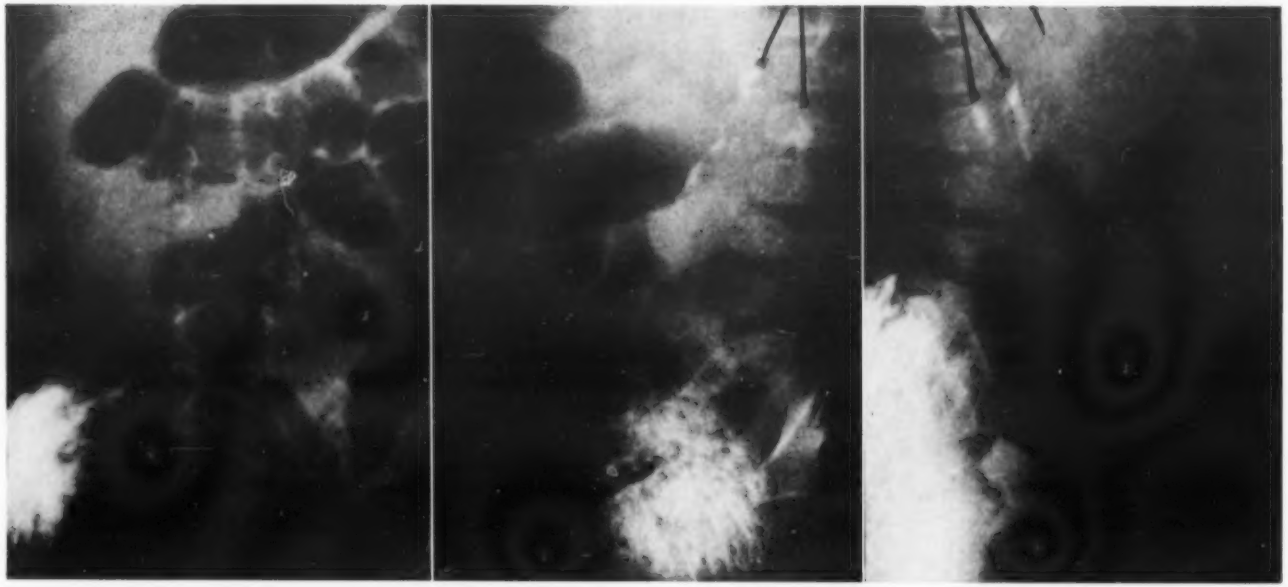


Fig. 1A.—Schematic representation of a transverse section of the abdomen at the level of LI. (Modified from Corning after Braune, Lehrbuch der Topographischen Anatomie, Achte-Neunte, Auflage, Wiesbaden, 1919, Verlag von J. F. Bergmann, p. 471.)

Fig. 1B.—Angle board with variable degree of angulation (picture posed, therefore no protective apron or gloves worn by nurse).

injected previously, has been far advanced or even completed.

The second point imposes a severe limitation on these methods: In infants who have been ill for some time and frequent periods of heat, and particularly during the hot and dry winds which are part of the regular climatic inconveniences in wide parts of the globe.



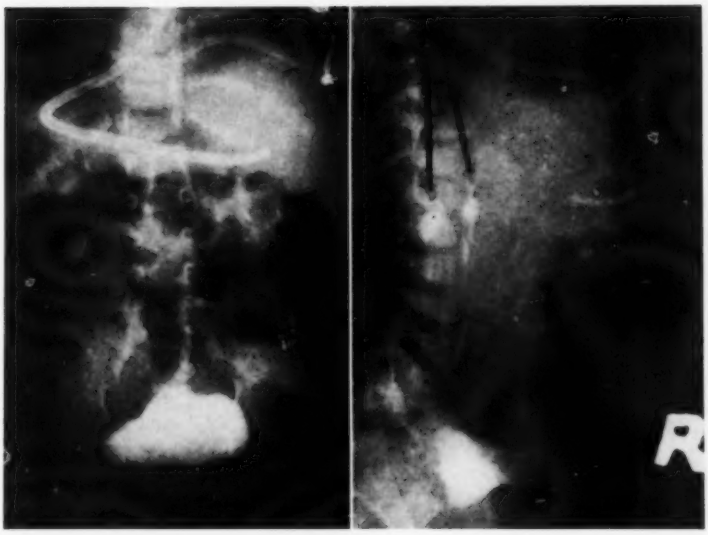
A. *B.* *C.*

Fig. 2.—Case 1, N. V., male, 3 months old. Pulmonary tuberculosis. Intramuscular pyelography. No preparation of patient.

A, Anteroposterior projection shows 10 minutes p.i. bilaterally the kidney cavities, on the left, however, obscured by gas-filled intestinal loops.

B, Left posterior-oblique view shows right kidney (closest to film) in front of spine, the left one more posterior. Kidney cavities are distinctly seen.

C, Right posterior-oblique view. Left side closest to film, left kidney seen in front of right one.

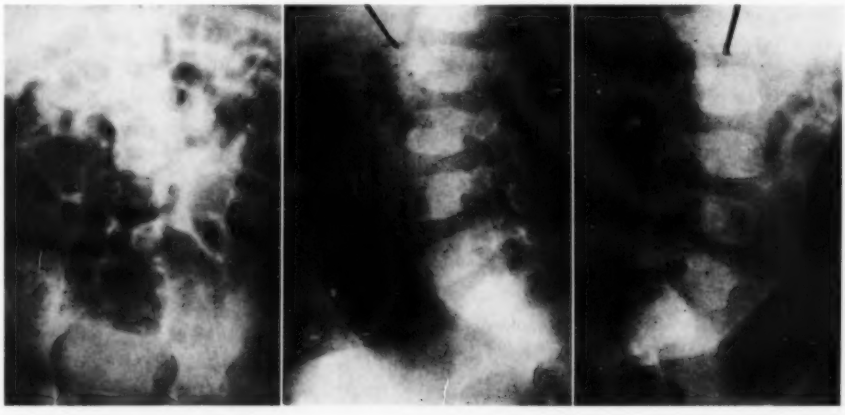


A. *B.*

Fig. 3.—Case 2, M. Y., female, 5 months old. Multiple growth disturbances. Intramuscular pyelography. No preparation of patient.

A, Anteroposterior projection shows cavities of right kidney. View of left kidney region obscured by intestinal gas.

B, Left posterior-oblique view (right kidney closest to film) shows distinctly two normally functioning kidneys.



A. *B.* *C.*

Fig. 4.—Case 3, G. M., male, 2½ years old. Differential diagnosis included renal vein thrombosis, polycystic kidneys, hydronephrosis, and tumor.

A, Anteroposterior projection. No excretion seen due to excessive intestinal gas.

B and *C*, In both posterior-oblique views there is excretion from the left side only, which appears to be normal.

At operation: right renal vein thrombosis with hydronephrosis.

IMPROVEMENT OF RADIOGRAPHIC PROCEDURES

A method which permits a truly satisfactory investigation of kidneys and urinary tract in infants by way of descending urography is tomography.[9] Its application, however, is obviously limited, because not every clinic or hospital, and smaller hospitals in particular, have a tomograph or even a tomographic attachment at their disposal. We have, therefore, tried to improve the radiographic procedure by the following method:

Because the kidneys are situated retroperitoneally, intestinal gas does not obstruct the pyelographic picture in the lateral projection. This anatomical fact points the way to an improved and reliable method of demonstrating the dye-filled kidney cavities without recourse to complicated means of preparation of the patient or technical procedures.

Since in the true lateral projection the shadows of the kidneys are almost superimposed on each other, we have positioned the children at an angle of approximately 75 degrees in the right or left posterior oblique diameter (Figs. 1*A* and 1*B*). Thereby, the kidney closest to the film is projected upon the anterior part or even slightly in front of the vertebral bodies, while the kidney on the far side is projected upon the posterior part of the vertebral bodies or into the small arch formed by the posterior parts of the lower ribs.

Owing to the obliquity there is a possibility that sometimes the shadow of a loop or two of gas-filled intestine may be interposed, but, in our experience, this has not caused serious interference with a clear view of the kidneys.

Since this method of examination of infants in accordance with the described technique has been introduced in our department we have repeatedly had the opportunity of proving its value (Figs. 2, 3, and 4*).

It is certainly not possible to see in a lateral or oblique view of the kidney the same details, which are visible in the anteroposterior projection, when gas does not obscure the view. By the technique herein described we may, however, regularly determine whether there is excretion or not, whether the kidney is displaced or in normal position, and whether there is gross distortion of the kidney cavities. In other words, in the excretory urography of infants and children, the postero-oblique view is a reliable help in many cases, e.g., those suspected of congenital anomalies, tumors, cysts, hydronephrosis, thrombosis of renal vessels, or displacement of the kidney.

SUMMARY

For excretory urography in infants and children the postero-oblique views are recommended as a means of avoiding the difficulties presented by the usually great amounts of intestinal gas.

By a postero-oblique position of about 75 degrees both kidneys are demonstrated separately and unobstructed by the anteriorly situated, gas-filled intestine.

This method gives satisfactory information as to the condition of the kidneys which are in many cases investigated in these age groups.

*Only 2 normal cases and one pathological case are presented in the illustrations. They are used only to illustrate the described method and therefore only brief clinical notes are given.

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THE PEDIATRIC MANAGEMENT OF SCHOOL PHOBIA

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IT IS the purpose of this presentation to outline the psychiatric principles underlying effective pediatric management of the child with school phobia and to indicate the results that may be anticipated from a psychologically informed approach to diagnosis and treatment.

School phobia comes to the attention of the pediatrician early after its onset and prompt diagnosis and judicious treatment can have a decisive impact on its further course. It lends itself to the ready delineation of psychodynamic issues in the genesis of neurotic disorders in childhood.

It is a matter of some urgency that the pediatrician sharpen his psychological skills. The therapeutic advances of the past two decades have produced major shifts in the pattern of pediatric practice with behavior problems becoming an ever more important focus of the "new" pediatrics.[1] Moreover, if there is to be any fruitful consequence of the concept of preventive mental hygiene, it must find expression within the framework of pediatric practice in view of the pediatrician's strategic role in well-child care. The psychiatrist is, and of necessity will remain, the consultant whose aid is sought after breakdown has occurred. His contribution to prevention, both primary and secondary, will depend upon his success in communicating to his pediatric colleagues such useful information as may be employed appropriately in office and clinic practice.[2-4]

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THE PROBLEM

The child with school phobia has a dread of attending school, a dread which has no apparent justification in his school experience. Even in the instances in which an unpleasant school encounter may be related to the precipitation of the syndrome, the experience is likely to have been one to which other children have been exposed with, at most, only temporary distress. Moreover, efforts to change teacher, class, or school regularly prove ineffectual in relieving the symptoms.

The fear of school may not be at all overt. The presenting complaint may consist of any one of a wide variety of somatic symptoms, whose distinguishing features are their early morning onset, prompt subsidence as school attendance is avoided, and singular absence on holidays.

The child with school phobia is not, let me make it clear, a truant. The truant dislikes school, has usually been an indifferent scholar, and starts out as if to go to class, only to spend the day roaming the streets. He is

likely to compound his felony by ingenious devices to conceal his failure to attend. The child with school phobia, on the contrary, is almost always a good student, is frequently a model of deportment and has vocational goals for which schooling is required.* Rather than concealing his difficulty in school attendance from his parents, he alarms them with his dismay and turns to them for solace. Most often, he will refuse to leave his home during school hours for fear his disability will become known to the neighbors.

How, then, are we to understand this paradoxical behavior? The answer becomes apparent when we extend our observation to the family as well as the child. A study of the behavior of mothers of such children in a specialized nursery school revealed in striking fashion that the mothers clung to their children even more desperately than the children to them.[6] They hovered in constant attendance, intruded themselves on various pretexts into the children's play, resisted the teachers' efforts to ease them out of the playroom, and offered frequent and uncalled for "reassurance" to the children. It was not uncommon to note a child happily engaged with his group, rather unconcerned when mother announced that she was about to leave, until her unnecessarily prolonged and tearful good-byes let him know he was expected to cry. Once she left, he could usually be induced to dry his tears and re-enter the group activity. His mother, during the same period, was observed by the social worker to be pacing about fretfully in the waiting room, unable to be convinced that he would survive her absence.

Clearly, then, the basic issue is not *going* to the school, but *leaving* mother. We are dealing, not so much with a phobia, as with anxiety about separation.[7-9] This is most readily evident from direct observation in the nursery school but can be confirmed for older children by taking note of mother-child interaction in the clinic waiting room and by detailed questioning about family behavior during the separation process.[9]

This defines the crucial therapeutic task: to enable child and family to liberate themselves from excessively close ties that stifle emotional growth.

But before we consider treatment procedures, let us first ask ourselves why this rather remarkable behavior exists. After all, the mother has summoned the physician because she is distressed by her child's inability to leave her for school. How are we to believe that she is causing him to remain at home? It should no longer surprise us to discover that contrary motivations can exist at one and the same time within both mother and child. Recognition and understanding of this ambivalence are necessary if we are to be of assistance in correcting the problems it produces.

The mother, on the one hand, wishes her child to develop normally, to attend school, and to overcome his fears. On the other, she needs his close attachment to her. She mistakes his clinging for a demonstration of love. She, too, is afraid, just as he is afraid, that some unnamed catastrophe is impending. She calls in the physician because she recognizes

*In a survey of 41 children with school phobia, we found that none were defective, less than one tenth were of dull normal intelligence, and half were in the bright to superior range of intelligence.[8]

that her child's behavior is abnormal —but also because she is becoming resentful of the demands for her constant presence.

The child's symptoms are comprehensible as his response to his mother's ambivalent motivations. She may offer verbal reassurance that there is nothing to fear but does so in a tremulous voice that conveys her own anxiety. She "insists" he leave for school but does so in an unconvincing manner; her indecisive movements and her quavering voice make it clear that, really, he need not. Her anxious questions about how he feels offer him the clue that if he but complain of being ill, he will not have to face the dreaded separation from mother.

Why do these mothers—or, in some instances, fathers—need their children so closely tied to them? The pathogenesis of symptom formation may be rather stereotyped, as already indicated, but the underlying causes are as complex and intriguing as the human situation itself. The reasons will vary for each case and can be elicited only by sympathetic and perceptive inquiry. I can but allude, in oversimplified fashion, to a few representative case illustrations:

Barbara was born late in a childless marriage, after five preceding miscarriages. She was all her mother had so long sought and all she was likely ever to have. Her mother's coddling and constant caution about her safety created in Barbara a morbid preoccupation with illness and injury.

Sheila became her mother's "special" child when she was born shortly after the maternal grandmother's sudden death. It was her burden to fill an aching void. The symbiosis between mother and Sheila was idyllic until mother took her first vacation away from her daughter. Sheila could not be gotten to school while her mother was away. A delay at the airport in the arrival of the plane bringing mother home sent the child into a panic. Once mother arrived, Sheila clung to her avidly, fearing for her safety, and retaliating for being abandoned. Mother was immobilized by her guilt at having left her daughter.

Mrs. L. resented Allan's presence; his arrival had sealed the compact of a bitterly disappointing marriage. Her anger toward him was incompatible with her conscious ideals of motherhood. As a visible badge of her love, she surrounded him with a suffocating cloud of overprotection. Her fears for his safety were the projections of her own hostile impulses. Her frenzied attention created in Allan an insatiable appetite for proof of her devotion; his demands drove her to angry outbursts which frightened both of them by their enormity. Allan could not trust her out of his sight for fear she might not return; he punished her by demanding complete subservience to his whims.

Mr. R. relived through Peter the unresolved issues of his troubled childhood. He tried to experience vicariously, by providing it to his son, the ideal fathering he so avidly craved and had never received. So close were the bonds that when Peter complained of nausea, his father vomited. Peter had learned adroitly to manipulate his father by simulating illness to avoid unpleasant responsibilities.

Philip had become the sole source of satisfaction in his mother's empty marriage. Seduced by her constant hovering, he had abandoned any interests outside the home. As he approached adolescence, he became acutely anxious at the first dim perception of the erotic elements in their love relationship.

Examples could be multiplied. But perhaps the few cited will serve to illustrate the range and complexity of the human issues involved. More detailed case studies reported in the literature should be consulted to supplement these necessarily abbreviated vignettes.[9-15]

TREATMENT

It cannot be emphasized too strongly that treatment begins with a searching diagnostic evaluation. A careful history and a thorough physical examination will in most instances suffice to indicate to the physician that he is dealing with a school phobia; in some cases, however, special diagnostic procedures will be necessary before organic pathology can be excluded.* Once he has established to his own satisfaction that the symptoms are those of school phobia, the pediatrician must seek to identify the major issues in family life that have given rise to the symptoms, if he is to develop a plan to interrupt the pathological cycles and to support the healthy trends in parents and child. This need *not* require a psychiatrist in most instances. The pediatrician usually has some prior knowledge of the family; he has a considerable asset in the positive expectations the family bring to him as the physician who has treated other illnesses successfully. A sensitive and interested inquiry, based on familiarity with the issues likely to be found, will lead to the identification of the central conflicts.

*Positive evidence of psychopathology does not rule out the possibility of a concurrent organic lesion. To take a recent example, an obviously disturbed child with recurrent abdominal pain was referred for psychiatric treatment; pediatric workup and subsequent operation revealed hydronephrosis secondary to ureteral obstruction.

With diagnosis established, the central focus in management is *prompt return to school.* This may seem at first glance a hazardous undertaking with a child who displays panic at the prospect of returning to school. The physician, no less than the family, may fear the precipitation of an acute breakdown. In fact, however, this does not occur with adequate support to child and family. The reasons for this therapeutic emphasis and its success require discussion.

To begin with, the longer the absence from school, the more complicated is the process of return. Added to the child's initial fears are now somewhat realistic concerns about the amount of school work he has missed, the possibly unfriendly reception by his schoolmates and the embarrassment at facing his teacher. Moreover, he has learned to luxuriate in the extra attention and solicitude his symptoms bring (the secondary gain). He has been denied normal growth-promoting experiences at school and instead has remained in the very situation which had produced his difficulty in the first instance. The fact that the adults around him are sufficiently alarmed to agree that he is unable to leave home serves to convince the child that his fears are real. It is as though all conspire to avoid facing the actual source of the symptoms by accepting their displacement on to school.

In addition, failure to insist on prompt return feeds neurotic patterns within the family itself. Mother continues to get such gratification as is provided her by the child's clinging. If the physician compounds the

problem by recommending a home teacher, then motivation for change will have been considerably diminished. Once the child has a home teacher and can continue his academic progress, there is less pressure within the family to alter a situation which has become rather comfortable. Indeed, the few failures we have experienced with elementary school children have been in those instances where uninformed physicians have provided medical certification for the child to remain at home. When the records of a group of such children were examined several years ago in the Baltimore school system, it was found that all of them had been at home for at least one year and several for as long as 3 years at the time the survey was undertaken.[16]

It is a common-sense rule in dealing with fears that the sooner the individual can be persuaded to expose himself to the situation in which his fear developed, the more readily does he overcome the fear itself. One recalls the baseball player who is inserted in the lineup immediately after he has recovered from being hit by a pitched ball, lest he become "ball shy," or the recommendation that a person who has been in a driving accident take the wheel as soon as he can in order not to allow a deep-seated reluctance to drive to develop. This principle holds in the case of a child with school phobia. Insisting that he return to school means to the child that the physician believes him capable of returning. This provides the only effective reassurance.

Before developing a specific plan for return to school, one must take into account the severity and duration of the syndrome. With an incipient or merely threatened school phobia, firm guidance of the parents on the necessity of regular attendance will usually suffice to abort development of a full picture. For a child who has remained out of school for some time, a realistic program must be geared to the problem he provides at school and to the strength his parents are able to muster. The physician should communicate with the school social worker or principal. Obviously, if one is to call for forceful return of the child to school, as may be necessary in some instances, the school must be prepared to follow through in retaining the child in class.

In dealing with the school, it is important at the outset to establish a collaborative relationship. The teacher may be apprehensive that the physician regards her as responsible for the child's difficulty. She may feel a sense of guilt that she has somehow failed the child or may be angry that he did not find her classroom sufficiently inviting to remain. If the physician states his understanding of the dynamics of school phobia as a home rather than a school problem, he immediately puts school personnel at ease. What the school is able to do will depend upon the skill and experience of the teacher. A new or insecure teacher, who may be very reluctant to receive a crying child in her classroom, should not have this burden thrust upon her. If one feels that the child is not ready for independent return to school but should have his mother in attendance for a period of adjustment, then one must have a teacher

who will not find the presence of the mother in her classroom threatening to her. All of these issues should be discussed frankly with the principal or social worker and a specific plan for the particular case developed. We have not hesitated, in those instances when we felt no progress was being made by the parents toward returning the child to school, to recommend to the school that the matter be brought to the attention of the Juvenile Court. It is not that we would recommend that a child with school phobia be committed to a training school; it is rather that, for some families, it is necessary to invoke the authority of the court to indicate forcefully that school attendance is compulsory. In almost every instance in which we have resorted to the use of the court, the child has been brought by the parents to school before the court hearing was held.

The mode by which a child is to be returned to school will then vary with one's estimate of the severity of the problem and the attitude of the parents and the school personnel. Possible ways of managing the situation vary from simple insistence upon return for incipient cases to such techniques as: having the mother remain with the child in the classroom for the first few days of return with a schedule developed for her gradual withdrawal; having the child remain in the principal's or counselor's office until he is able to attend class activity; and having the child visit his teacher after class is dismissed in order to get his homework. I should like to reiterate our finding that placing a child on home teaching is a grave error in the treatment of school phobia. As Klein[8] pointed out, it is essential that the child enter the school building itself. This then becomes the bridge to full attendance.

The plan should be discussed fully with the child. He should be told that the physician considers him able to return and that return is obligatory. School attendance has been set by civil authority to which the physician must defer as well as the child. The child may be given some choice as to the schedule by which his return is to be effectuated but he has no choice as to whether he is to return. At the same time, discussion with the parents should focus on their behavior during the period in which the child's return is being discussed and carried out. They should be helped to recognize that their own anxieties will be communicated to the child if they themselves are not convinced of the correctness of the position they are taking. This concept can be made more meaningful by citing examples of their behavior in the office and at home.

A moment's reflection will serve to make it clear that the general method described is most easily applied to the young child whose physical behavior can be controlled by his parents. The problem is of an order of magnitude several times greater in the adolescent child.

It should hardly need emphasis that the management of school phobia is not a matter of a single consultation. The physician must be available to child and family at regular intervals in order to provide the support necessary during the trying period of readjustment.

RESULTS

For the purpose of this paper, all of the cases registered in our clinic between 1952 and the present have been summarized. To these cases have been added 10 seen at a specialized nursery school and an additional 10 seen in consultation elsewhere. As shown in Table I, of the 67 children, 48 were successfully returned to school.

TABLE I. THERAPEUTIC RESULTS

AGE (YEARS)	SUCCESS	FAILURE	TOTAL
Less than 11	39	5	44
11 and older	9	14	23
Total	48	19	67

A sharp distinction is evident, however, between the 44 children who were less than 11 years of age at the time the diagnosis was made and the 23 who were 11 years of age and older. Roughly speaking, this is the division between the elementary school and junior and senior high school levels. Of the elementary school age group, 39 or 90 per cent were successfully returned to school. This figure, however, underestimates the percentage of success that should be obtained. Of the 5 failures, 3 occurred in children who were certified by physicians in the community as unable to attend school, thus rendering further help ineffectual.

In contrast, of the 23 children of junior high school age, only 9 or 45 per cent had been successfully returned to school at the time the survey was undertaken. Among the 14 failures, there were 4 children who were schizophrenic. Seven came from families that were grossly decompensated, "multiple problem" families. These children were repeating patterns of defeat and inadequacy that had been evidenced repeatedly by either one or both parents.

The sharp contrast in results between the elementary and the high school age groups indicates that the adolescent with school phobia is not a suitable problem for pediatric management but requires referral to a psychiatric clinic. This is evident not only from the study of clinical results but from review of the patients themselves. These children were far more disturbed than the younger group, who were reacting to current family situations. In the adolescents, the symptoms reflected a severe disturbance of psychological structure resulting from years of exposure to a distorted family environment.[17]

We might then revise our diagnostic and therapeutic appraisal with these findings in mind. School phobia is a syndrome but not a disease in itself. It is a symptomatic manifestation of an emotional disturbance which may vary from a situational reaction to a severe character neurosis or even a psychosis.[11, 13, 14, 17] For the severely disturbed adolescent, extensive psychotherapeutic work is required if a successful result is to be obtained.

It may be argued that psychiatric or pediatric first aid for the elementary school child might result in disappearance of the symptoms but leave the basic pathological problem untouched. If this be true, one would anticipate a recurrence of the school phobia or a substitution of other psychiatric symptoms. In order to assess

this question, we obtained follow-up information on all cases seen at our clinic between the years 1952 and 1957.[5] There were no cases lost to the study. The average duration of the follow-up period was 3 years and varied from 15 months to 6 years. Table II presents our findings.

TABLE II. OUTCOME OF 41 CASES OF SCHOOL PHOBIA FOLLOWED FOR AN AVERAGE PERIOD OF 3 YEARS

AGE (YEARS)	ATTENDING SCHOOL REGULARLY	UNABLE TO ATTEND REGULARLY	TOTAL
Less than 11	24	3	27
11 and older	5	9	14
Total	29	12	41

As can be seen, the results are essentially the same as those obtained at the time treatment was terminated. The 29 successful cases were without major difficulties as judged by reports from their parents and schools. Three of the children exhibited some academic difficulties; 2 of these had I.Q.'s in the 85-90 range. Three others had become aggressive rather than fearful or withdrawn. We cannot say what these patients will be like 10 or 15 years from the present but at least over the follow-up period the results appear to be enduring. There has been no indication of symptom substitution of magnitude sufficient to suggest that the therapeutic emphasis had been incorrect.

These results become understandable when we recognize how major an accomplishment it is to enable a child afraid of school to return and overcome his difficulty. His pathological dependence on his parents has been diminished. His parents have been enabled to permit him to resume a more normal life as they have turned to a more gratifying relationship with him. He has had the opportunity of interaction with his peer group. In essence, what has been accomplished is that his growth potential has been allowed to flower. Is this not the very process by which most normal children, all of whom have difficulties to overcome in the course of life, move on to greater maturation? The striving for health, given a reasonably challenging environment, is a potent therapeutic factor in the hands of the physician skilled in its guidance.

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THE OUTCOME OF PREGNANCY IN DIABETIC WOMEN

II. Analysis of Clinical Abnormalities and Pathologic Lesions in Offspring of Diabetic Mothers

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IN PART I of this study evidence has been brought forward indicating that in addition to the pregnancy wastage, the morbidity of the offspring of diabetic mothers is also significantly higher than in the sample of normal controls. Here, we are mainly concerned with the analysis of clinical abnormalities and pathologic lesions encountered in the offspring of diabetic mothers.

The material is the same as outlined in Part I and consists of 18 stillbirths (Caucasian 7, Negro 11), 13 infants who died during the neonatal stage (Caucasian 4, Negro 9), and 6 surviving but abnormal offspring (Caucasian 2, Negro 4); all of these occurred in 157 pregnancies of 48 diabetic women. To allow comparison, the results of clinical examinations as well as the pathologic findings in the offspring of prediabetic mothers and in the sample of normal controls are also presented.

RESULTS

Stillbirths.—In the diabetic sample, of 18 stillborn infants, 13 were full term and 5 were prematurely born; 3 were delivered by cesarean section and 15 by natural means. The control of the diabetes at the time of delivery was poor in 11 and satisfactory in 7 of the mothers; 3 mothers had complications of pregnancy in the form of polyhydramnios and 1 had uterine bleeding during the fifth month of gestation. Autopsy was not performed in 6 of the stillbirths; in 7 of the remaining 12, the postmortem examination was not conclusive owing to pronounced maceration. In 5 infants postmortem examination was satisfactory but failed to reveal significant abnormality in 3; the fourth infant had congenital heart disease (stenosis of tricuspid valve and agenesis of cusps) and in the fifth a hemorrhage in the posterior cranial fossa was encountered.

Among 78 pregnancies in the prediabetic women there were 4 stillbirths; 2 of these occurred in full-term and 2 in premature infants. In the 2 full-term stillbirths autopsy was not performed. One 7-month-old premature infant showed no significant abnormality on postmortem examination and the second premature stillbirth was macerated.

There were 3 stillbirths among 249 pregnancies in the normal control mothers. Two of these were premature (7 months of gestation) and postmortem examination was normal

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apart from immaturity of the internal organs. The third stillbirth was a full-term infant, but autopsy was not performed.

Thus, the main abnormality in the stillborn infants of prediabetic and normal control mothers in whom postmortem examination was carried out consisted of prematurity. In stillbirths of diabetic mothers, however, the significant pathologic lesions included congenital heart disease in 1 and hemorrhage in the posterior cranial fossa in 1.

Neonatal Deaths.—Among 13 diabetic offspring (one set of twins) who died during the neonatal stage, 4 infants were delivered by cesarean section between 36 and 38 weeks of gestation. Of the 9 spontaneously delivered infants, 3 were premature and 6 were full term; 1 of the premature infants became severely jaundiced (mother Rh positive) and died on the third day after birth. The control of maternal diabetes at delivery was poor in 7 pregnancies and satisfactory in 6. Complication of gestation by hypertension was present in 1 mother, and premature separation of the placenta occurred in 2. Death occurred within 24 hours from birth in 9, within 3 days in 2, and within 4 weeks in the remaining 2 offspring. Postmortem examination was not performed in 2 infants. The autopsy findings in the remaining 11 patients were as follows: (1) Pulmonary atelectasis which was commonly associated with hyaline membranes and congestion of internal organs were the only major findings in 8 patients. (2) Major congenital malformations were present in 2 infants. One of these had congenital heart disease in the form of tetralogy of Fallot, but unfortunately the central nervous system was not examined; the second infant had multiple congenital malformations consisting of polydactylia, micromelia, diaphragmatic hernia, malformation of ears, and hypoplasia of brain (rudimentary cerebral hemispheres). (3) Massive cerebral hemorrhage was found in 1 baby.

There was only 1 neonatal death among 78 pregnancies of prediabetic mothers. The infant was born at term but was very inactive and hypotonic and died 30 minutes after delivery. The obstetrician thought that this mother had oligoamnios. Unfortunately, autopsy was not performed.

Among the 249 pregnancies in the normal matched controls, there were 9 neonatal deaths. Of these, 6 infants were premature, delivered between 30 and 36 weeks of gestation, and 3 were full-term infants. The state of health during pregnancy was normal in all but one mother who had elevation of systolic blood pressure ranging from 150 to 190 mm. Hg. In 4 of 9 infants postmortem examination was not done. In the remaining 5 the main abnormality consisted of prematurity alone in 2, prematurity and hemorrhage into the adrenals in 1, and pulmonary atelectasis in 2. Thus, the majority of the neonatal deaths in the offspring of normal control sample occurred in premature infants and the main autopsy findings were limited to prematurity and pulmonary atelectasis.

Postmortem examination of diabetic offspring who died during the neonatal stage revealed hyaline membrane disease of the lungs in 8, severe congenital malformation in 2, and lethal cerebral birth injury in 1.

Clinical Abnormalities in the Surviving Offspring of Diabetic and Normal Control Mothers.—Since the aspect of morbidity among the offspring of diabetic mothers is of special interest in this study, a brief summary of clinical and laboratory findings on these patients will be given, preceded by classification of the major findings. Of 157 gestations in the diabetic mothers, there were 6 abnormal surviving children; this constitutes an incidence of 3.8 per cent (or 7.6 per cent of the total of 79 surviving offspring). Four of these offspring were born spontaneously at term, 1 was delivered by cesarean section at 37 weeks of gestation, and 1 was a 7 month premature infant born by natural means. The control of diabetes at the time of delivery was satisfactory in 3 and poor in the remaining 3 mothers. One pregnancy was complicated by polyhydramnios. Two infants showed a moderate degree of asphyxia at birth.

On the basis of the main clinical and laboratory findings, these 6 abnormal children can be classified in the following three categories: congenital malformation—3: (a) gross skeletal malformation—1, (b) congenital hydrocephalus—1, (c) microphthalmia and hypoplasia of retinae—1; epilepsy and birth injury to the brachial plexus—1; mental deficiency and defective motor skill—2; total—6.

CASE REPORTS

CASE 1 (W. D., a 6-year-old Negro boy).—Delivery took place by cesarean section at 36 weeks of gestation. The control of diabetes was poor throughout the pregnancy and in addition polyhydramnios was present. At birth a number of congenital malformations involving the skeleton and tongue were encountered. All internal organs were normal. The initial development of the infant was slow, but at the age of 6 years his I. Q. (Stanford-Binet Scale) was 91. Although his speech was indistinct as a result of malformation of the tongue, he could be understood. There was a congenital absence of the right foot as well as the absence of the first two toes in the left foot. His left hand was normally formed but he had only the thumb and the little finger on the right hand. As can be seen in Figs. 1 and 2 the abnormalities are the result of primary agenesis.

CASE 2 (P. D., a 20-month-old Negro boy).—The patient was delivered spontaneously at term. The mother required 30 U. of insulin daily but the course of her pregnancy was normal. At birth the baby was inactive and the respiratory movements were poor. Excessive enlargement of his head was noticed by 6 weeks of age and his subsequent development was retarded. We investigated him in the hospital at 20 months of age, at which time his head circumference was 55 cm. and the anterior fontanel was widely open, measuring 5 by 6 cm. He had a moderate degree of cerebral diplegia and his developmental age was 9 months at the chronologic age of 20 months. The electroencephalogram showed diffuse unspecific abnormality and the pneumoencephalogram disclosed a marked degree of communicating hydrocephalus (Fig. 3).

CASE 3 (B. S., a 3-year-old Caucasian girl).—This infant was born spontaneously at term following a normal course of pregnancy. Maternal diabetes was poorly controlled. The baby weighed 5 pounds and 6 ounces, was of a small stature, and had a pronounced bilateral microphthalmia. Her initial mental and motor progress were considerably retarded. However, when she was examined at the age of 30 months her

FIG. 1.—CASE 1. Congenital absence of second, third, and fourth fingers; the thumb and the little finger are malformed. The radiogram shows normal radius and ulna but there are only 4 carpal bones present. These 4 bones and the metacarpals have atypical appearances, although the internal osseous structure is normal.

FIG. 2.—CASE 1. Congenital absence of the right foot and of one third of the lower leg. The left leg and foot are normally formed except for the toes. The big and second toes are absent, and the remainder are rudimentary.

developmental age was improved and she approached the level of a 26-month-old child. Both her eyeballs were microphthalmic and the vision was grossly deficient. She also exhibited constant, oscillatory movements of her eyeballs. The retinae were thin and the optic nerves hypoplastic. Otherwise, neurologic examination did not reveal any significant abnormality. The clinical diagnoses were: microphthalmia, hypoplasia of retinae and optic nerves, and mild retardation of development.

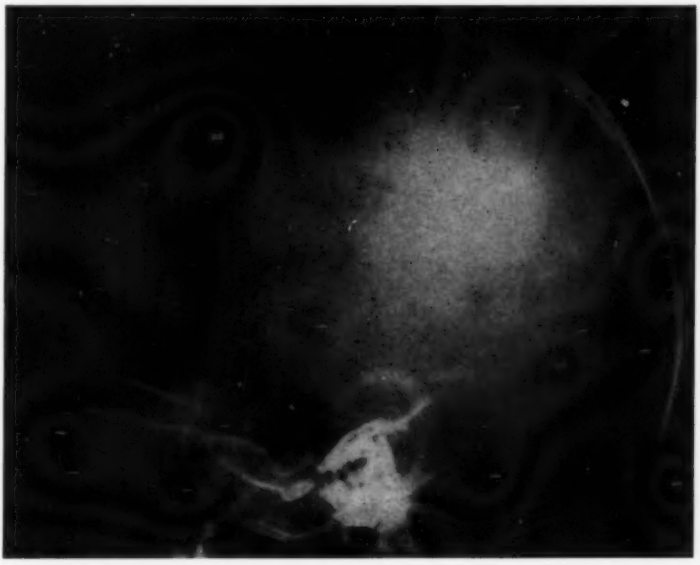

Fig. 3.—Case 2. Pneumoencephalogram, right lateral projection, note marked dilatation of both lateral ventricles. A small amount of air is present in the basilar cisterns and in the subarachnoid space. In other projections the third and fourth ventricles and also the Sylvian aqueduct were outlined. The skull is enlarged and the anterior fontanel is slightly bulging.

Case 4 (T. C., a 10-year-old Negro boy).—The patient was born spontaneously at term. The maternal diabetes was under satisfactory control at the time of delivery. However, the baby appeared moderately asphyxiated at birth and exhibited right brachial plexus palsy. Between 2 and 4 years of age he had 8 convulsions. When examined at 10 years of age there was atrophy of the right upper arm which was the result of birth injury; there was no other evidence of neurologic abnormality. He attended third grade in a public school and his mental state was considered to be low average. The clinical diagnoses were: epilepsy and sequelae of birth injury to the right upper brachial plexus.

Case 5 (B. M., a 9-year-old Caucasian boy).—During pregnancy maternal diabetes was controlled with diet alone but the mother's urine gave positive tests for sugar on several occasions. The boy was born about 10 days postmature and weighed 11 pounds, 11 ounces. He was edematous and slightly cyanotic at birth, but subsequently his respirations were satisfactory. Retardation of development was noticed shortly after birth and he was hospitalized at the age of 9 years when his I. Q. was 37 (Stanford-Binet). Although he had no focal paralysis of the extremities nor any sensory deficit, his motor skill was definitely poor.

Routine laboratory tests and the electroencephalogram were within normal limits. Our clinical diagnosis was mental deficiency with imperfect motor development.

CASE 6 (R. N., an 8-year-old Negro boy).—The control of maternal diabetes was satisfactory. The birth was spontaneous but premature, occurring in the seventh month of gestation. Following delivery the infant was mildly asphyxiated and required resuscitation. Retardation of development was observed from the early months of life. At the age of 8 years he was hospitalized for general investigation. He was found to be dull; his I. Q. (Stanford-Binet) was 62. Neurologic examination was normal except for a moderate degree of clumsiness during the performance of movements requiring skill. Routine laboratory tests and the electroencephalogram were normal; the pneumoencephalogram disclosed a symmetrical ventricular system of average size. Our clinical diagnosis was mental deficiency and imperfect motor development.

As was already mentioned, there were 2 abnormal, surviving offspring in the sample of 78 prediabetic pregnancies. This constitutes an incidence of 2.5 per cent. However, 1 of these offspring most likely suffered from idiopathic epilepsy which was prevalent in her family. The following are brief histories and findings in these 2 children.

CASE 7 (B. J., a 13-year-old Negro boy).—The family history was negative for neurologic or mental disorders. The mother felt well throughout her pregnancy. The birth was spontaneous and at term. The establishment of respirations was delayed for a few minutes. Subsequent physical condition of the infant is said to have been good and he was gaining weight satisfactorily. However, his mental development was retarded and when he was hospitalized at 13 years of age, his I. Q. (Stanford-Binet) was 30 and his motor skill was deficient. The routine laboratory tests, electroencephalogram, and pneumoencephalogram were all normal. The clinical diagnosis was mental deficiency and imperfect motor development.

CASE 8 (an 18-year-old Negro girl).—The course of pregnancy and delivery were normal. At the age of 3 months the infant had her first convulsions. These have continued at irregular intervals, mainly coinciding with negligence in taking medication. Two of the patient's blood relatives also suffered from epilepsy. Detailed neurologic examination was negative and her intelligence was normal. She liked school and her marks were slightly above average in her class. The clinical diagnosis was epilepsy, probably of the idiopathic type.

Of the 249 pregnancies in the sample of matched normal controls, there was only 1 abnormal surviving offspring; this constitutes an incidence of 0.4 per cent.

CASE 9 (P. N., a 5-year-old Negro boy).—Apart from occasional vomiting the mother felt well throughout her pregnancy. The delivery was spontaneous and at term but the infant appeared inactive. Examination at 2½ years of age revealed mild cerebral diplegia. However, his developmental age approached quite closely his chronologic age except for the motor performance which was handicapped by a slight weakness. The clinical diagnosis was mild cerebral diplegia of undetermined etiology.

Thus, of the 2 abnormal offpsring in the group of prediabetic mothers, one was mentally defective and the second had epilepsy probably of the idiopathic type. The only abnormal child in the sample of normal controls had mild cerebral diplegia of undetermined

etiology. Three of the 6 abnormal surviving children born to diabetic mothers had lesions classified as congenital malformation, 1 had epilepsy and birth injury, and the remaining 2 were mentally defective with imperfect motor skills of undetermined nature.

COMMENT

If the major abnormalities encountered in stillbirths, in infants dying during the neonatal stage, and in the abnormal surviving offspring of diabetic mothers are added together, they can be classified as follows: pulmonary atelectasis and hyaline membrane disease alone—8; congenital malformations—6; birth injury—3; mental deficiency with poor motor skill—2; total—19.

These data do not represent the true rates of pathologic lesions in the offspring of diabetic mothers, inasmuch as autopsy examination did not include all infants who died and in a considerable proportion of macerated stillbirths a comprehensive pathologic diagnosis was not possible. Nevertheless, these findings provide important indicators of the main causes of perinatal mortality and also they suggest the possible underlying pathology in the surviving but abnormal offspring. In general, the following five categories can be distinguished: (1) stillbirths, without obvious major lesion, although some infants were edematous; (2) pulmonary hyaline membrane disease; (3) congenital malformations; (4) birth injuries; (5) mental deficiency.

Group 1.—Stillbirths constitute a considerable proportion of the perinatal deaths. Most of the deaths occur during the last weeks or days of gestation and generalized edema of the nonmacerated babies is a common finding. The cause of the increased rate of stillbirths in diabetic mothers remains largely unknown. Serious disturbances of tissue respiration as well as electrolyte and hormonal imbalance are presumed (Farquhar,[3] 1956; Aakerren, 1954) but definite proof is lacking.

Group 2.—Pulmonary hyaline membrane disease commonly occurs in the infants of diabetic mothers. Although premature infants, particularly when born by cesarean section, are especially predisposed, the formation of abnormal membranes in air passages occurs also in full-term, spontaneously born infants. Even though the state of the baby at birth can be satisfactory, a respiratory distress may develop within a short time and the majority of these infants die within 15 hours from birth. Postmortem examination reveals absorption atelectasis and the presence of hyaline membranes in the lungs. In our diabetic series atelectasis and pulmonary membrane disease accounted for the deaths of 8 out of 11 of the infants dying during the neonatal period. This finding fully supports the opinion of other investigators and calls for increased efforts in research which is directed at prevention of hyaline membrane disease in newborn infants.

Group 3.—Congenital malformations are usually the result of arrested or disturbed differentiation of embryonic tissues during the early stage of organogenesis. There is a great number of noxious factors which may lead to congenital malformations, if these factors happen to act during a particularly sensitive stage of development.

In this relation experimental investigations are particularly illuminating. Pertinent to the conditions observed in the diabetic mothers are studies by Duraiswami[2] (1950) who produced skeletal malformations in chick embryos by injecting insulin in the egg within the first 48 hours of incubation. Using the same agent, Lichtenstein and co-workers[7] (1951) produced developmental anomalies in rat embryos. Hyperglycemia and acidosis can also disturb fetal homeostasis (Reardon and co-workers,[8] 1955; Heller and Diekmann,[3] 1957) and lead to malformations. It is of interest also that Frazer and Fainstat[4] (1951) were able to increase the incidence of congenital malformations in a susceptible strain of mice by the administration of cortisone.

It must be stressed, however, that the anomalies of development occur only in a proportion of the exposed animals. This fact may indicate that operation of other factors than those experimentally introduced may be necessary to disturb differentiation of the embryonic tissue or that the stage of development during which a specific malformation can be produced is very short. Our studies on irradiation of pregnant mice reveal that the difference in gestation of 6 hours is sufficient to increase or decrease greatly the rate of malformations, depending on the stage of pregnancy when the embryos were exposed. If present, genetic predisposition to malformations is also important.

In the series of 157 pregnancies of diabetic mothers we encountered 6 conspicuous congenital malformations. Two of these concerned major skeletal anomalies in the forms of aplasia and dysgenesis. To produce such anomalies, the disturbance of development must have occurred between 4 and 9 weeks of gestation. One infant who had skeletal deformity also showed severe hypoplasia of both cerebral hemispheres which can also originate during the same gestational period. In 2 other offspring congenital cardiac anomalies were present. The teratogenetic period leading to various cardiac anomalies is rather long and it may extend from the fourth to sixteenth or more weeks of gestation. The fifth offspring had microphthalmia and hypoplasia of retinae and optic nerves; her motor and mental development were also slightly retarded. The last of the 6 patients had a communicating hydrocephalus (Fig. 3) which became obvious at 6 weeks of age. This infant had a normal birth and no evidence of meningitis during the neonatal period. This type of hydrocephalus is frequently of congenital origin with the overt manifestations becoming manifest in the early weeks or months of postnatal life. The basic abnormality may be confined to the leptomeninges or to the mechanisms underlying absorption of the cerebrospinal fluid. On the semantic basis it could be argued that this patient should not be included in the category of malformations. However, in view of the lack of evidence of other pathologic lesions in brains examined with similar types of hydrocephalus, it was decided to consider him here on a tentative basis.

In general, it can be said that with the exception of the last patient, the embryonal development must have been disturbed prior to the tenth

week of gestation to produce the abnormalities observed. The immediate cause of the increased rate of congenital malformations in diabetic offspring remains unsolved, although hypoglycemia, ketosis, and hormonal disturbances can be suspected and each of these has experimental support (Duraiswami,[2] 1950; Hicks,[6] 1953; Reardon and co-workers,[8] 1955, and others).

Group 4.—Birth injuries of a mechanical type were present in 3 offspring. One was a stillborn infant who had massive cerebral hemorrhage, the second died within 15 minutes from birth and had bleeding in the posterior cranial fossa, and the third sustained brachial plexus palsy; he also has epilepsy. It appears highly probable that the increased incidence of birth injuries in offspring of diabetic mothers who are delivered spontaneously at term is related to oversized babies and to such factors as disturbance of tissue respiration and generalized edema of the fetus.

Group 5.—The presence of mental deficiency in 2 of 6 abnormal surviving offspring as the only major finding is an interesting finding but very difficult to interpret. Although these children had a comprehensive investigation in our hospital, no specific underlying lesion could be demonstrated. It is known that certain types of cortical malformations as well as minor anoxic changes in the brain may defy detection even with the aid of electroencephalography and pneumoencephalography. On the other hand, it is known also that in a proportion of mental defects even detailed postmortem examination may fail to reveal the presence of structural lesions in the brain. Each of our patients with a mental deficiency (Cases 5 and 6) could have suffered from anoxia or birth injury, although this could not have been proved by the clinical and laboratory tests at the time of our examination.

If one were to attempt to answer the question, what constitutes the major abnormality encountered in the offspring of diabetic mothers, the likely answer would be complex. There are at least three different types of clinical abnormalities: congenital malformations, birth injury, and mental deficiency of as yet unspecified pathology. The underlying anatomic lesions may originate during the early or late stage of gestation, during the process of birth, or even during the first days of life, all being a result of different causative factors. This is well demonstrated by the finding of increased rates of congenital malformations, birth injuries, oversized babies, generalized edema, hypertrophy of the islands of Langerhans, and pulmonary hyaline membrane disease.

SUMMARY

In addition to an increased fetal loss and high perinatal mortality, the offspring of diabetic mothers also have an increased risk of morbidity as compared to the normal controls. Of 157 pregnancies in 48 diabetic women, 6 offspring were abnormal. This constitutes an incidence of 3.8 per cent of all pregnancies and 7.6 per cent of the 79 surviving children. In the matched controls the abnormal surviving offspring constituted only 0.4 per cent of 249 pregnancies.

Three of the 6 abnormal surviving children born to diabetic mothers had

severe congenital malformations, 2 had mental deficiencies, and 1 had sequelae of birth injury and epilepsy. Of the 41 offspring of diabetic women who were stillborn or died during the neonatal stage, 16 had comprehensive postmortem examination at which the following findings were observed: pulmonary hyaline membrane disease in 8 patients; congenital malformations in 3; cerebral birth injury in 2; and no gross, demonstrable lesion in the remaining 3. Factors possibly pertaining to the increased fetal loss and to the higher rate of morbidity among the offspring of diabetic mothers are discussed.

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Medical Progress

THE MECHANISM OF ANTIBODY-ANTIGEN REACTION AND ITS IMPLICATION IN ALLERGIC AND IMMUNOLOGIC STATES

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SOME years ago a new mechanism for antibody-antigen interaction was advanced. It arose from a study of the inhibition of the enzymic activity of a crystalline yeast enzyme (alcohol dehydrogenase) by specific antibody.[1, 2] It was also supported by a study of the precipitin reaction between the antibody and the same antigen[3, 4]; the mechanism proposed stems from the premise that when an antibody molecule reacts with an antigen molecule there is produced in the resulting complex a simultaneous alteration of the surface configuration of the two component parts. New groups are exposed and the spatial relationships of the existing groups altered. This could result in the creation of new antigenic sites on the complex that involve either (a) the antigen surface, (b) the antibody surface, or (c) their adjoining surfaces. Specific antibody would then form against the new antigenic sites of this complex. When the antibodies so formed react with their respective sites, a new complex is formed with further alteration of the surfaces of the antibody and antigen. In like manner, further complexes are subsequently formed. This process could continue until the original antigen disappears from the body of the subject or when no further alteration in the surface configuration is obtained. This process is represented in graphic form in Fig. 1, where the formation of new antigenic sites is shown on the surfaces of the antibody and the antigen. Only one out of a number of possible primary sites on the antigen and on each of the antibody molecules is represented in this illustration.

This concept is supported by the following findings which were obtained from our quantitative and kinetic studies of the precipitin reaction with the use of three different antigens; ovalbumin, bovine serum albumin, and yeast alcohol dehydrogenase. It was the study of the kinetics of inhibition of the enzymic activity of the latter, as related to the precipitin reaction, which ultimately gave rise to this concept. In all instances, rabbits were used for immunization.[1-4]

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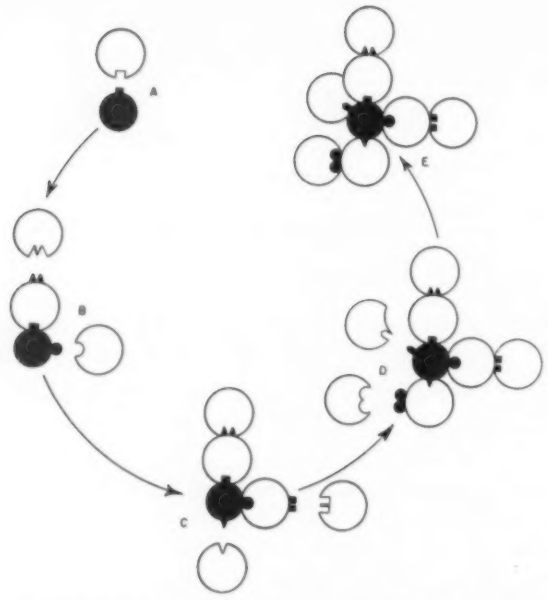

Fig. 1.—Shows the proposed sequence of events according to the concept discussed in this paper. Only one primary site out of a number of possible ones is represented in the graph. Furthermore, only one modified site out of a number of possible ones is depicted to occur on the antigen and antibody after interaction with the respective site. When the first antibody reacts on the antigenic site, both antibody and antigen are shown to be altered simultaneously. Antibodies are then formed against these sites of altered configuration. This process continues as further sites appear on the antigen and reacting antibody. We have graphically shown only one antibody as a minimum, reacting with another antibody which has been modified by antigen. Four antibodies have been chosen also arbitrarily to react with antigen directly.

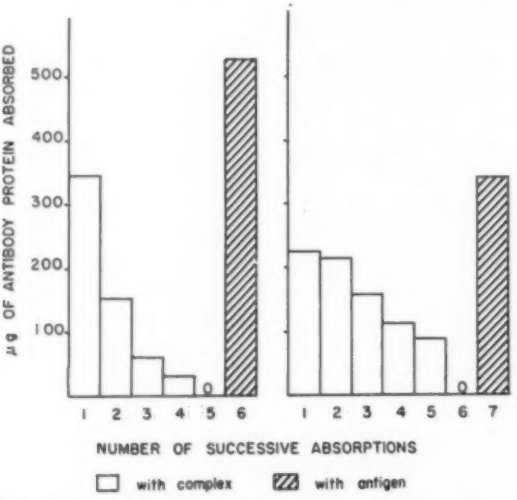

Fig. 2.—The selective absorption of antibodies from antiserum to ovalbumin (left) and antiserum to yeast alcohol dehydrogenase (right) by antibody-antigen complex. Absorption was performed exhaustively by 1 mg. of antibody-antigen complex, followed by antigen. Incubation time in each case was 2 hours at 25-30° C. and 1 hour at 0-4° C.; pH 8.25.[2, 3]

The results show that antibody to complex can be exhaustively absorbed leaving behind enough antibody in the supernatant that reacts with antigen.

1. It is possible to absorb exhaustively a sample of antiserum with a given antibody-antigen complex, or two different complexes one at a time, yet in each case leave behind antibodies that react only with free antigen.[1-3] This is shown in Fig. 2. The only reasonable explanation for this is that new antigenic sites are formed on the complex following antibody-antigen interaction.

2. It is possible to fractionate antisera and obtain fractions that react only with antigen and other fractions that react only with antibody-antigen complex.[5-6] This further strengthens the conclusion that new antigenic sites are formed on the complex. These sites might appear *de novo* on the antigen surface, on the antibody, or on both.

3. Rabbits immunized against rabbit antibody-antigen complex obtained from other rabbits show antibodies in some animals that do not react with antigen but react only with complex. The rate of this reaction with complex is unaffected by extreme antigen excess.[6] This indicates that the antibody generated by the complex is directed against the antibody portion and not against the antigen. Were the antigen involved, some inhibition would have been obtained. In other animals similarly immunized, antibodies to antigen can also be demonstrated. These can be absorbed exhaustively by antigen, leaving behind antibodies that react with complex.[5, 6] Recently, we have been able to show that when rabbits are immunized, each with complex prepared from its own antiserum and antigen, they generate antibodies that react with the specific antibody-antigen complex and not with the antigen.

4. It is possible in a large complex to aggregate many more antibody molecules on an antigen of smaller size than could possibly be accommodated because of steric hinderance.[3-6] This indicates that a certain number of antibodies must attach to other antibodies on the complex at various stages.

Further supporting evidence can be cited from other laboratories:

A. In their studies on the disappearance of antibody from circulation following antigen injection, Dixon and associates[7] were able to show that as many as 75 to 100 molecules of antibody were accounted for by each molecule of antigen.

B. Robert and Grabar[8] investigated the SH of some antibody-antigen complexes. They found a liberation or exposure of previously unreactive globulin SH groups in all the systems studied. Following the reaction of antibody with antigen, the SH groups in the antibody, which were previously unavailable to the SH reagent, became exposed and, therefore, available for amperemetric titration. This furnishes good chemical proof for configurational change in the antibody following antibody-antigen interaction.

C. Ishizaka and Campbell[9] showed that there is a significant increase in levorotation upon antibody-antigen interaction. This indicates that either or both antibody and antigen suffered configurational change. Using a trihaptenic dye, resorcinol triphenylarsonic (1,3-dihydroxy-2,4,6-tri-(p-(p-azophenylazo)-phenylarsonic acid)-benzene), which is not optically active, they showed a considerable increase in levorotation of the antibody upon reaction with the dye hapten. This is a

direct proof with physical measurements of configurational change in the antibody molecule upon interaction with antigen. It appears, therefore, that there is sufficient and adequate supporting evidence for this concept based on biologic, immunochemical, chemical, and physical measurements.

It is pertinent to remark at this point that the concept implies that an antibody molecule, normally considered familiar and nonantigenic, may in the same animal, as a consequence of altered configuration caused by union with antigen, be rendered unfamiliar, foreign, and thereby antigenic.

It should be pointed out also that until recently the closest experimental approach to this problem was to immunize rabbits with antibody-antigen complexes prepared from antisera of other rabbits that have been immunized with the same antigen. The interpretation that could be placed on these findings is that an antibody could be generated in one rabbit against an antibody from another rabbit. Had this been shown not to be the case, the concept would fall to the ground and other interpretation would have to be sought for. Recently, however, it became possible to show that a rabbit can form antibodies against a complex prepared from its own serum. Several rabbits were immunized with weekly subcutaneous injections of 10 mg. of ovalbumin for 7-10 weeks. Their antisera were stored in the frozen state. Over two years following this, each of the four survivors was then immunized with antibody-ovalbumin complex prepared from its own stored anti-ovalbumin serum. The complex was prepared at equivalence. Two subcutaneous injections, each consisting of 2 mg. of complex, were given a week apart. Two of the four rabbits yielded antibodies in their sera that reacted only with the specific complex and not with antigen.[12]

A corollary for this already exists, as it has been shown that an animal can produce antibodies against a component obtained either from its own tissue or from the corresponding tissue of another animal of the same species. Thus, testicular suspensions or sperm of one guinea pig, mixed with adjuvants and injected into another guinea pig, produce specific tissue antibodies and specific tissue damage. The stimulation of antibody formation and the pathologic lesions observed are also produced when the guinea pig is similarly injected with its own sperm or with testicular suspensions prepared from one of its own testes.[10] In like manner, rabbits immunized with thyroid extracts of other rabbits elicit an antibody response to such extracts. Rabbits also produce such tissue-specific antibodies when immunized with extracts of their own thyroids obtained by complete or partial thyroidectomy.[11]

Consequently, the results obtained in our laboratory and by others as enumerated above make it mandatory to invoke the presence of antibody to the antibody portion of the complex in the same antiserum. It is difficult to obtain as satisfactory an explanation on any other basis.

In view of this and the evidence emanating from the various approaches discussed above, it is fair to conclude that the principles involved in this concept have all the support that is experimentally feasible at this time. The demonstration that a configurational change in the antibody upon interaction with antigen or a complex hapten is on firm grounds. No such

direct evidence can be shown for the antigen. One is fully justified in surmising, however, that the likelihood is great that the protein antigen should be subject to the same forces that apply to the antibody protein.

Other than its importance in the chemistry of protein-protein interaction, the concept of configurational change in antibody-antigen interaction should have interesting and challenging implications in immunologic and allergic states. We have extended this concept to apply to these states largely on theoretical grounds and as a basis for future experimental investigation.

ALLERGIC AND IMMUNOLOGIC STATES

An allergic state is a rather vague descriptive clinical condition. An individual who reacts in an unfavorable manner after contact with a foreign substance is said to be sensitive or allergic to that substance. The individual may have already had previous but symptomless contact with the foreign substance. In this case, the phenomenon is likely to be an immunologic one. On the other hand, the individual concerned may not have had any previous contact with the now offending substance. For example, a small percentage of individuals may show an untoward "sensitivity" reaction to salicylates, penicillin, sulfonamides, etc., during the first exposure to the drug. In such instances no immunologic basis need be assumed, as this entity can readily be explained on the same basic principle, viz., that the foreign substance reacts with a particular tissue component in such a way as to alter its surface configuration, thereby materially affecting its biologic function.

We have termed a substance that produces this effect upon first contact an allergenoid, in contradistinction to an allergen, which does so after the individual has had previous contact. In order to elucidate the pertinent points of this discussion, it is necessary to recall that, within the same species and with the exception of uniovular twins, no two individuals possess immunologically similar characteristics in their respective tissues. This has been amply confirmed by homologous tissue and organ transplants. On a molecular level, this means that in the main most individuals show strict individuality and variability with respect to homologous proteins. Rabbit globulins have been recently shown to have individual immunologic specificity within the species.[13, 14] It follows then that the same functional type of protein molecule may differ, to some minor extent, in configuration and other physical properties from one individual to the other.

Let us assume, for the sake of this argument, that a certain tissue enzyme has a particular affinity for penicillin. The configuration of this enzyme differs in different individuals. Depending on this type of configuration, it may then combine with penicillin with varying degrees of molecular distortion, the latter being very marked in some and negligible in others.

A person who reacts to penicillin upon the first exposure would, according to this concept, possess a certain specific configuration of this particular enzyme, quite unlike the configuration of the same enzyme of other individuals. The configuration is such that an interaction with penicillin occurs and alters the specific function of

this protein. The interference with this function gives rise to symptoms that may very well be indistinguishable from symptoms characteristic of the typical immunologic type of allergy. At no time, however, would one be able to show any evidence of any immunologic reactions.

The interaction of penicillin with this enzyme, however, may not be so drastic as to interfere with its function and result in symptoms. It may only alter its surface configuration sufficiently to render it antigenic. Antibodies would then be formed against the antigenic surface of this hitherto normal protein. These antibodies would react with it and cause a serious distortion in its configuration. The result would be a drastic interference in the function of that enzyme. The very same symptomatology would then be expected to ensue, since the same enzyme is affected. In the latter instance this represents a true immunologic type of allergy, and antibodies may be demonstrable directly, by serum transfer, or by cellular transfer.

Either of these two phenomena, caused by an allergen or allergenoid, may involve any organ in the body, and typical lesions in the skin ranging from angioneurotic edema to frank eczema may appear. Should the lungs be involved, symptoms of asthma might develop. If the blood is affected, hemolysis might result. In the first instance, antibodies can never be recovered as they are never formed. In the second instance, an immunologic reaction should in some manner be demonstrable.

This latter type of immunologic reaction may not be demonstrable by in vitro test. It can be shown more commonly by tissue sensitivity reactions such as skin testing. The demonstration of circulating antibody by conventional techniques of flocculation or complement fixation may be successful only if antibodies directed against the antigen used are present in serum. In some instances, these circulating antibodies are not demonstrable with the use of these in vitro techniques. In vivo tests have been devised, however, that demonstrate a local reaction after skin testing. So far there has not been a satisfactory explanation for this occurrence. According to this concept the explanation would be that the antibody which is present in this serum is not directed against the presumed antigen. In vitro tests with this antigen would not be expected to show a positive flocculation or complement fixation and ordinarily they do not. The true antigen is a tissue protein, possibly an enzyme of some sort, that has been rendered antigenic by combination with the assumed (but truly false) antigen. The individual's free and unassociated enzyme protein ordinarily would not cross-react strongly with the antibody so formed. However, the antibody would naturally have some affinity for this normal and unmodified enzyme. This is expected if the modified and antigenic site formed by association with the foreign substance is not too alien in configuration with reference to the corresponding site on the free unassociated enzyme. In this case, even in the absence of this foreign substance and presumed antigen, a reaction between the antibody and tissue enzyme may result in some measure of association

between the two molecules. This association would account for the long-lived residence of the antibody at the site of the skin test, i.e., the prepared passive-transfer area. It would also explain why so often one observes a local reaction in the skin following the injection of the allergic serum during passive transfer.[15]

Serum passive transfer is negative in many instances of allergy of the tuberculin type of hypersensitivity. Here again this observation falls within the scope of the concept brought forth. The antibodies that are formed are simply capable of stronger cross-reaction with some normal tissue protein which has been rendered antigenic by association with tuberculin or some other product. They are therefore absorbed away from the circulation through strong association with the particular protein in tissues. This association is not in this instance detrimental enough to the biologic activity of the tissue to cause damage. A positive and successful passive transfer, therefore, could occur only by transfer of cells that carry or form the antibody and not by serum transfer. The serum would be for all practical purposes devoid of antibody at all times except periodically when the latter is in transit from the cells that form it to the tissue that fixes it specifically.

There are experimentally and clinically numerous manifestations of allergy ranging from the violent reaction of anaphylaxis to the less violent asthmatic attacks and the relatively mild form of cutaneous reactivity. The difference may well depend on the degree of damage to the particular tissue and to the type of tissue concerned. There are many suggestions that symptoms of anaphylaxis may be due to extensive vascular damage. In this instance, the antigen reacts with some component of vascular tissue to give rise to an antigenic complex, the principal antigenic part of which is the vascular tissue component. Antibodies reacting with that portion result in the destruction or inhibition of the activity of that tissue. Histamine, 5-hydroxytryptamine, or proteolytic enzymes may, as a result, gain entry to the circulation and aggravate the condition through a generalized pharmacologic effect.

From the preceding discussion, one can derive a simple formulation of the concept pertaining to allergic states, which now guides our present investigative efforts. It implies that an allergen or an antigen entering the animal system reacts with some tissue component to effect a configurational change in that component and render it antigenic. Antibodies are then formed against the particular tissue component which may react in one of three ways:

A. The antibodies may require the presence of the antigen to produce the specific site on the host's tissue component. This would imply an absence of an injurious cross-reaction with the free, unassociated, and therefore unaltered, tissue molecule. The typical allergic state as exemplified by ragweed allergy would fit this category.

B. The antibodies, once formed through the stimulus of the antigen, may not require the presence of the latter to react with the tissue. In other words, the antibody formed against the altered tissue component

can actually cross-react with the unaltered component so strongly as to produce damage to the tissue in question.

In the two categories cited above it is necessary to have the antigen for the continuous production of antibody. In both instances, the damage caused will be self-limited and depends on the level of antibody which in turn would depend on the presence of antigen for its maintenance.

C. In the third category, the pathologic state would only be triggered by the antigen or toxin. This in turn would result in tissue breakdown. Disorganization of cellular structure may result in the production of new antigenic sites by autolysis or by permitting strong association between molecules hitherto not associated. The result of this association would presumably be a structural alteration to produce antigenic sites in an otherwise normal molecule. The type of damage caused would be expected to be self-perpetuating. The cellular destruction resulting from the action of this autoantibody would continuously produce the necessary antigenic determinants which in turn stimulate further autoantibody formation. Lupus and some progressive neurological diseases may fall into this category.

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Clinical Pathological Conference

The Children's Medical Center
Boston, Mass.

Sidney Farber, M.D., *Editor*
John M. Craig, M.D., *Assistant Editor*

A 22-month-old Negro girl was admitted to The Children's Medical Center because of persistent fever. She was well until 5 days before entry, when she first became febrile. Four days before entry, she became lethargic and anorexic and vomited several times. Her fever continued. She was seen by her physician who gave her tetracycline for pharyngitis and otitis media. Three days before admission the respiratory rate became elevated, the fever remained unabated. No cough or diarrhea was noted. One day before admission she was seen in the Medical Clinic, where her temperature was found to be 104° F., rectally, pulse 200, and respirations 40 per minute. The physical examination disclosed a mild infection of the tympanic membranes and a slight mucoid discharge from the nose. No other positive findings were elicited.

Laboratory examination disclosed that there was a 4 plus reaction for albumin in the urine; the specific gravity was 1.015; there was an occasional leukocyte in the spun sediment. Urinary tests for sugar and acetone were negative. The hemoglobin was 14.0 Gm. per cent and the peripheral leukocyte count was 19.2 thousand per cubic millimeter. The leukocyte differential count was 70 per cent polymorphonuclear leukocytes and 30 per cent lymphocytes. A chest roentgenogram was reported as normal.

The only significant episode in the history was an infection of the umbilicus in the newborn period which responded to antibiotic therapy.

The patient was seen here in the Outpatient Department, and aspirin, penicillin, and streptomycin were prescribed but because she did not improve she was admitted to the hospital the next day.

At the time of admission, the temperature was 104° F., the pulse was 200, and the respiratory rate was 60 per minute. The blood pressure was 90 mm. Hg systolic, and 50 mm. diastolic. The child was acutely ill. She had an injected pharynx and a tender liver, which was felt 2.0 cm. below the costal margin. The abdomen was otherwise soft and nontender, with normal peristaltic sounds. The heart was not enlarged and no murmurs were heard.

The examination of the urine revealed a trace of albumin but no other abnormality. The hemoglobin was 12.0 Gm. per cent. The peripheral leukocyte count was 30.0 thousand per cubic millimeter, with a differential count of 90 per cent polymorphonuclear cells and 10 per cent lymphocytes. A preparation for the demonstration of sickle cells was negative. The serum chemistry determinations were direct bilirubin 0.6 mg. per cent and total bilirubin 1.7 mg. per cent; serum albumin 4.3 Gm. per cent; globulin 1.6 Gm. per cent, and the nonprotein nitrogen 34 mg. per cent. The liver flocculation tests showed cephalin flocculation, 1 plus; thymol flocculation, 0; and thymol turbidity, 2 plus. The serum febrile agglutinins were negative; the heterophile reaction had a plus-minus reading at a dilution of 1:14. Blood cultures taken on three occasions gave no growth. A repeat chest roentgenogram was normal. An electrocardiogram displayed a nodal tachycardia and an incomplete right bundle branch block, with marked RST and T wave changes.

The patient was continued on the penicillin and streptomycin therapy. Twelve hours after admission, the liver was felt 4.0 cm. below the costal margin and at 24 hours, 6.0 cm. The cardiac silhouette was now widened. The patient was given digitalis. During the second hospital day, the temperature remained elevated; antibiotic therapy was changed to chloromycetin and erythromycin. The respirations were grunting, with flaring of the alae nasae. The heart rate was 120 per minute, with a poor quality of the heart sounds and a gallop rhythm; the liver remained enlarged and tender. On the third hospital day an intravenous pyelogram demonstrated a normal excretory pattern, but a rounded cystic shadow, continuous with the liver, was seen in the right upper quadrant. On the fourth hospital day, the patient was transferred to the Surgical Service where an operation was performed.

DISCUSSION

DR. ORVAR SWENSON.*—First, I might pick out some of the important points in this child's story. We have evidence of infection with high fever, a fast pulse rate, 4 plus albumin in the urine, a high and rising leukocyte count, and negative blood cultures. There was evidence of cardiac failure, with a very rapid heart rate, a widening cardiac shadow, an enlarging tender liver, and a slowed pulse rate with digitalis.

We are all quite curious about the radiographic films, and we might see these now.

DR. BRIAN P. O'MALLEY.—Films taken on the second hospital day of the second examination showed an enlarged cardiac silhouette, but clear lungs. A rounded shadow at the anterior lower edge of the liver overhung the kidney (Fig. 1). Those taken four days later showed no apparent change An intravenous pyelogram preoperatively showed normal bones and kidneys.

DR. SWENSON.—This is a clearly outlined spherical mass extending anteriorly below the liver, is it not?

DR. O'MALLEY.—Yes.

DR. SWENSON.—With the reported physical findings and negative chest

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roentgenograms, a case for Staphylococcus pneumonia must be abandoned, but I believe that a severe infection was present and that the heart rate of 200 was the result of a toxic myocarditis. The severity or even the presence of cardiac failure may be questioned because the reported increase in the size of the liver may actually have been the x-ray-demonstrated mass increasing in size. Furthermore, by the roentgen studies the liver did not seem to be enlarging.

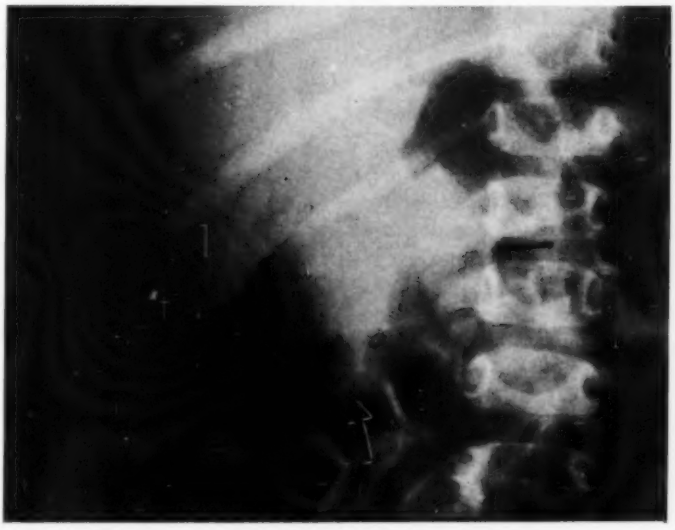

Fig. 1.—Radiograph of abdomen. A full rounded shadow is seen just below the liver edge.

With cardiac failure and evidence of infection, bacterial endocarditis must be given consideration as a tentative diagnosis. Three negative blood cultures are strong evidence against this.

One must consider what localized infections would give tenderness in the region of the liver. The first to be considered is liver abscess. This is very rare, is usually secondary to some generalized infection, and, because of the hematogenous spread, is usually multiple. In only a third of the cases does jaundice occur, so the absence of jaundice does not rule it out, yet mobility of the diaphragm and the presence of a shadow below the liver cannot be completely accounted for on this basis.

Amebic abscess should be considered, but the absence of a history of diarrhea would induce me to discard that as a possibility.

A choledochal cyst is a possibility in this age group. However, those of any size are commonly associated with jaundice, which was not a symptom in this patient. I have never seen acute infection of such a cyst, but it may be possible.

Tumors of the liver may be associated with secondary infection. Some lymphangiomas may project outside the liver to give a shadow, and these

may become secondarily infected. The infected ones I have had experience with have been fairly readily controlled with chemotherapy, but since they often have a poor blood supply they may habor quite a raging infection within their confines.

Going outside the liver, subphrenic abscess might be considered, although I do not think one should consider it seriously since it is usually preceded by some other intra-abdominal infection. All of the fifteen cases reviewed here by Dr. Ladd and Dr. Swan were secondary. The clear chest films and freely moving diaphragms almost completely eliminate this diagnosis in this patient.

Subhepatic abscess is a definite possibility; appendicitis in this age group is rare and diagnosis is difficult, usually being made after perforation occurs. Statistically such an abscess is not a prominent possibility but must be considered. The feature against it is that the shadow on the film is too clearly and sharply outlined for a subhepatic abscess secondary to a perforated appendix. Occasionally, with malrotation, a perforated appendix may form a primary abscess under the liver edge. In such a situation there is usually a great deal of gastrointestinal upset, which was not present in this case.

Perinephric abscess is a possibility; and may occur without any pre-existing renal disease. Though the clinical picture may resemble this case, more commonly these abscesses tend to develop gradually. The children with perinephric abscess whom I have seen tend to flex the leg and resent having it straightened. In a number of these cases there may be abnormalities on the pyelogram. A fluoroscopic study of the motion of the kidney may be of value in accumulating evidence for and against perinephric abscess. The shadow seen here is definitely anterior. This location and the absence of a psoas sign make perinephric abscess unlikely.

The other known source of lesions outside the liver in this area is the gall bladder but gall bladder disease is rare in children of this age.

Most gall bladder disorders in children are associated with blood dyscrasias, such as sickle cell anemia. These patients have soft pigment stones which may give rise to obstruction.

Dr. Hudson has published reports of young children with acutely inflamed gall bladders. I have always assumed that some minor congenital malformation of the valves of the cystic duct was present to account for the obstruction and subsequent inflammation of the gall bladder in such cases.

I think acute hydrops of the gall bladder can explain the clear outline seen in the roentgen film. I believe, also, that this child had a severe infection, the intensity of which was due to its being sharply confined within a structure, either the gall bladder or, as a second possibility, a tumor such as a lymphangioma. Finally, I think this child was in cardiac failure and may have had a congenital heart lesion, but I do not feel strongly about this last.

Dr. James M. Baty.—I remember one of the children of whom Dr. Swenson spoke, was observed as a 4-month-old baby for several hours for a possible intussusception, but at operation was found to have a huge inflamed gall bladder which was removed.

Dr. Craig.—Just to confuse you, Dr. Swenson, two days after the operation the child's temperature was still

101° F., and she had a peripheral leukocyte count of 31,000 per cubic millimeter. At this time, a diagnosis of rheumatoid arthritis was entertained.

DR. SWENSON.—Such cases as this one, with continuing symptoms but no localizing signs of infection, can be very perplexing. We had one such child, 18 months old, with a diffuse vasculitis, on whom an exploratory operation was performed for a perinephric abscess, but who died with a coronary thrombosis.

DR. MERRITT LOW.—I have never seen appendicitis in a child under 2½ years of age without acetone in the urine or more symptoms referable to the gastrointestinal tract at some time in the illness.

DR. FARBER.—Dr. Hauck, would you tell us about the electrocardiogram.

DR. ANNA HAUCK.—The most striking thing about this electrocardiogram is that the tachycardia, which is at a rate of 170, is not a sinus rhythm. The P-R interval is extremely short, a tenth of a second, which classes it as a nodal tachycardia. This is not the usual nodal tachycardia since the P waves are not those described when the atria are activated by a retrograde impulse. Since the P waves are quite normal, the lesion must be a "coronary nodal tachycardia" arising in the area of the coronary sinus. There are very definite T wave abnormalities: the T in Lead I is very flat and the ST segment is markedly depressed. These changes can occur secondary to tachycardia, or they may represent myocardial disease. Such RST and T wave changes have been associated with dilatation of the gall bladder; the most recent experimental work, however, has shown that it occurs in dogs only when the coronary supply is impaired.[1] The heart rate of the patient returned to 120 after digitalization. I would presume that much of our confusion arose from this arrhythmia. Whether she had underlying myocarditis or perhaps even some impairment of the coronary supply, I do not know. Postoperatively, the electrocardiogram returned to normal.

DR. SWENSON.—I think it would be worth saying that often, in patients with rheumatic fever there is lengthening of the P-R interval, which gives me a little comfort.

DR. CHARLES A. JANEWAY.—We never see rheumatic fever at this age, but rheumatoid arthritis is found, and may give a confusing picture.

The finding of an atypical rash and heart failure in this patient is strongly suggestive of this diagnosis. Cardiac failure has usually been associated with pericarditis in our cases of rheumatoid arthritis, but not invariably. The prompt return to normal patterns in the electrocardiogram would tend to rule out heart failure as a cause of the enlarging liver.

DR. CRAIG.—Does this rapid return to normal of the T waves tend to make you dismiss myocarditis as an etiological factor?

DR. HAUCK.—Not entirely.

DR. JACQUELINE A. NOONAN.—I saw this child when she was in the hospital and she did have some congestive failure at the time that she was digitalized, not only on the basis of an enlarged liver, but also because she had marked flaring of the alae nasae. She improved some in oxygen alone, and the cardiac rate decreased when

she received digitalis and oxygen, although the abdominal trouble became more obvious. It was extremely difficult to examine the abdomen because the baby was very irritable and cried constantly. It was not until she was given Nembutal that we could really examine the abdomen, and then it became quite obvious that there was a mass in it.

DR. SAMUEL R. SCHUSTER.—On the Surgical Service we were confused by this baby. The resident considered everything that Dr. Swenson has mentioned, except gall bladder disease. After seeing the x-ray, he thought that the child had gall bladder disease and an exploratory operation should be carried out. I do not think that we understand everything that went on here, despite the fact that a large, distended, but not grossly inflamed gall bladder was found at operation. Adults with gall bladder disease often have symptoms of coronary heart disease, and this may be the case here. As far as the postoperative temperature is concerned, I still do not know how to explain it.

DR. SWENSON.—One may see cholangitis persisting for several days after hydrops of the gall bladder, which may not respond to antibiotics. This might be the explanation for the continuing fever.

A FOURTH-YEAR STUDENT.—The students believed that the cardiac signs and symptoms were secondary to the cystic and obviously inflammatory right upper quadrant mass. Other diagnoses that were discussed were hepatic abscess and perinephric abscess.

DR. KEVY.—Dr. Swenson, what is the incidence of jaundice in children with cholecystitis?

DR. SWENSON.—I think it is extremely rare, because the incidence of common duct stone is very low. Gall bladder disease is seen most commonly in association with hemolytic syndromes. Cholecystitis with hydrops does occur in the very young. Such patients, I think, have some congenital abnormality.

A PHYSICIAN.—Dr. Swenson, how do you rule out an anomalous fetal lobe in the liver which has been reported to produce a roentgenologic picture similar to that of a gall bladder?

DR. SWENSON.—Very simply. I didn't even think of it.

A STUDENT.—Could this possibly be a viral infection involving both the liver and the heart?

DR. SWENSON.—I consider that a diagnosis of desperation. We have too many positive findings indicative of a specific localized process.

DR. CRAIG.—This was a hydropic gall bladder. It measured 10 by 5 cm. and when opened had no obvious bile, but was full of mucoid material. There were no stones in the gall bladder. On microscopic examination, it did show evidences of inflammation (Fig. 2) to a greater extent in the wall than in the epithelium lining the gall bladder. The wall was tremendously edematous, there was fibrin along the external surface, and there were numerous polymorphonuclear leukocytes, eosinophils, and some mononuclear cells throughout the wall. The cultures from the gall bladder content were sterile.

This child, then, had a *subacute cholecystitis*. The biopsy was taken

from the liver. I think it was taken from the gall bladder bed, so that it is not a very representative section, but it did show some degree of congestion. There was no intrahepatic cholangitis.

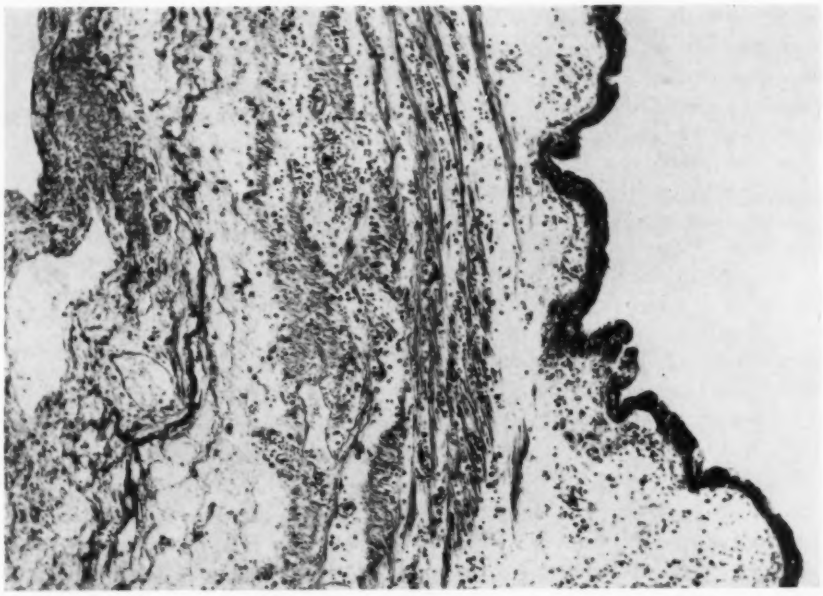

Fig. 2.—Photomicrograph. Gall bladder. The wall of the gall bladder is markedly thickened, edematous, infiltrated with inflammatory cells, and impregnated with fibrin. (Toluidine blue and eosin. ×150.)

The child did very well postoperatively, except for the fever for the first few days. She was seen again in the clinic a week or so after she was discharged. The heart rate was normal and the liver had receded to 3 cm. She has not been seen since that time, so we presume she is well. We believe, then, that this is an example of a physiologic involvement of the heart, secondary to nervous disturbance arising in the gall bladder.

Cholecystitis in childhood differs from that which one sees in adults. The average age of children with cholecystitis is between 8 and 10 years. They do not have evidence of dyspepsia or chronic complaints of a digestive nature. Unlike adults, the males are more frequently affected. It is interesting to note that jaundice has been such a prominent feature in children; some 26 to 45 per cent in various series have jaundice, as opposed to about 8 to 10 per cent in adults, and curiously enough not all of those with jaundice also have stones. About 60 per cent of the children in our series have had stones, while between 80 and 90 per cent of adults are so affected. Hydrops also occurs frequently without evidence of stones, as mentioned by Dr. Swenson. One wonders how often, as may be the case in this child, there may be a cholangitis or a choledocholangitis with obstruction of the cystic

duct, or even the common duct, on an inflammatory basis, with development of jaundice.

It is interesting that a number of these children have had a primary diagnosis of appendicitis including 2 in our own series. The correct diagnosis was made only because of the awareness and intelligence of the surgeon who, finding a normal appendix, looked to see if there was anything wrong with the gall bladder.

On the other hand, some of the cases of cholecystitis in children have been misdiagnosed as hepatitis. There have been 2 cases reported of rupture of the gall bladder with generalized peritonitis in which a primary diagnosis of hepatitis was made. One of the cases which Dr. Hudson reported occurred in a 1-month-old child. We had one instance where, in a 3½-year-old child, there was jaundice with choledochal stones for 2½ years before he was operated upon.

DR. FARBER.—Dr. Swenson will undoubtedly want to know, Dr. Craig, why this child had this condition at the time she did.

DR. CRAIG.—That I do not know.

Speaking of rheumatoid arthritis, both the tests for C-reactive protein and the serum latex coagulation test for rheumatoid arthritis were done postoperatively, and they were both normal. So, at least on a laboratory basis, she did not have rheumatoid arthritis.

DR. JANEWAY.—I think the reference connecting coronary disturbances and gall bladder disease is very interesting. I would suppose that, to the cardiologists, this merely represents a case of paroxysmal tachycardia which was initiated by disease in this area. We have seen this occur with trauma in the mediastinum on one or two occasions. I remember one of Dr. Swenson's patients who was operated upon for a tracheoesophageal fistula had severe paroxysmal tachycardia.

DR. SWENSON.—Those patients respond very dramatically to digitalis. It is one of the best uses of digitalis I know.

DR. JANEWAY.—Well, I think this child did, but we were confused by the fact that she was very, very uncomfortable. I am sure the child also had an enlarged gall bladder which was thought to be an enlarging liver.

DR. FARBER.—Dr. Swenson, would you close, please?

DR. SWENSON.—There must be some congenital malformation in connection with the cystic duct in this patient. I can explain it in no other way. Certainly that area is most prolific in abnormalities. I would assume that there was some difficulty with the cystic duct and it became pretty well occluded because there was no bile-stained material within the gall bladder, the secretion which it contained arising from its own wall. Some hollow organs secrete more mucus as they become increasingly tense, which augments the difficulties.

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Comments on Current Literature

VIRUS CROUP

INFECTIONS of the respiratory tract constitute a major group among the illnesses of infants and children and, in the young child, croup can be a serious manifestation. The characteristic lesion is an inflammatory process involving the larynx, trachea, and bronchi. The gravity of the illness and the severity of the symptoms depend to a considerable extent upon the amount of edema of the vocal cords and the subglottic structures which accounts for the narrowing of the airway and the subsequent respiratory difficulty. Inflammation may extend also into the lower respiratory tract. In some instances stenosis of the air passages may be aggravated by membrane formation as is typical in diphtheritic croup. Respiratory embarrassment is the most common cause of death. Conventional bacteriologic studies are often reported as negative, or may reveal a variety of organisms—streptococcus, staphylococcus, pneumococcus, *Hemophilus influenzae,* et cetera.

Rabe[1] was among the first to point out the possible viral etiology of infectious croup and to suggest that in some instances the bacterial agents recovered might not represent the primary invasion. A study first reported in 1947 was prompted by "the considerable difference of opinion as to the etiologic role of the various bacteria found in association with the disease."[1] Rabe postulated that the majority of cases of croup are essentially viral in origin. He reached this conclusion on the basis of an extensive investigation of the bacteriology, pathology, and clinical course of 347 cases of infectious croup, grouping the patients into "three etiologic categories; namely, diphtheritic croup, *H. influenzae* type B croup, and so-called 'virus' croup." Of the 347 cases, only about 14 per cent could be shown to be associated with bacterial pathogens.

Rabe described the virus type of croup as distinct in its pathologic manifestations from croup due to *H. influenzae* type B, or to *Corynebacterium diphtheriae,* and as similar to viral influenza in the human subject and to laryngotracheitis in fowls. Clinically the disease appears to be progressive with a downward spread of the infection in the respiratory tract. Inflammation extending into various regions is expressed in such clinical forms of the disease as laryngitis, laryngotracheitis, or laryngotracheopneumonitis. Mortality increases as the disease spreads down the respiratory tract, and one of the most frequent severe complications of this type of croup is the occurrence of extra-alveolar thoracic air.

Developments within the past few years have brought these early observations into new significance. The consistent failure of antibiotic agents to influence the clinical course in this type of infection has paralleled the lack of significant bacterial agents cultured during the acute illness in these patients. While virus isolation had been attempted in some instances, it was not until 1955 and 1956 that the croup-associated viruses began to be isolated and identified. In the fall and winter of 1955 a widely disseminated viral agent appeared to be associated with croup or, in older children, with respiratory illnesses characterized by croupy cough, the manifestations depending to a large extent upon the age of the patient. At this time Chanock[2] reported the finding of a new strain of virus of the myxovirus type in cases of infantile croup. Somewhat later similar isolations were reported by Beale, Rhodes, and their associates,[3] and also by Cramblett,[4] cytopathogenic agents of this same type being isolated from infants and young children with laryngotracheobronchitis.

As the name implies, the myxoviruses are characterized by a special affinity for certain mucins.[5] The virus section of the International Nomenclature Committee has provided a short description of this group which includes the agents of influenza A, B, and C, Newcastle disease, fowl plague, and mumps. These viruses are similar in size, and have a group-specific soluble antigen. They have the quality of adsorption to and subsequent agglutination of erythrocytes, in some instances with hemolysis; later the virus elutes leaving irreversible alterations in the mucoprotein receptors of the red cell surface. The newly described hemadsorption viruses (HA viruses) belong to this myxovirus group; they are known to be associated with acute respiratory infections, pharyngitis, pneumonitis, and the like. Their isolation has been accomplished chiefly by means of the Vogel-Shelakov[6] technique which involves the use of monolayer monkey kidney tissue cultures to which guinea pig erythrocytes adsorb readily in the presence of these so-called hemadsorption viruses. With certain modifications in the technique these tissue culture preparations can be used for the detection of virus in material originating from throat swabs or from nasopharyngeal washings of patients showing acute respiratory disease.[7]

Significant studies of the hemadsorption viruses and other croup-associated viruses are being reported currently by Chanock and his associates,[8] a group of investigators who have been interested in the "respiratory viruses" for some years. In October, 1957, two new myxoviruses, hemadsorption viruses types 1 and 2, were isolated from the oropharynx of children. Subsequent investigations indicated that these viruses are of significance in respiratory-tract disease in children. The clinical findings in affected children included "a wide spectrum of respiratory-tract illness varying from rhinitis and bronchitis with or without fever through the relatively severe croup syndrome or bronchopneumonia." The newly isolated strains of virus exhibited the property of hemadsorption, and were capable of hemagglutinating both fowl and guinea pig erythrocytes. These two hemadsorption viruses (types 1 and 2) showed certain antigens in common

with the other myxoviruses, but were found to be serologically distinct from each other and from other known human myxoviruses. An evaluation of the data on 42 patients with infection due to type 1, and 50 patients with infection due to type 2 revealed considerable overlapping in the clinical manifestations, which included cough, rhinorrhea, and pharyngitis as major symptoms. More severely ill patients had respiratory distress or croupy cough. Pharyngeal erythema was a common physical sign, with the more severely ill patients showing dyspnea, abnormal lung findings such as rhonchi and râles, or signs of laryngeal obstruction. Part of the epidemiologic study[9] of the type 2 strain of hemadsorption virus included its transfer to human volunteers (adults), and an investigation of the range of severity of clinical manifestations in adults as compared with those in children.

A recent report by this group of investigators,[10] appears in the *New England Journal of Medicine* for July 2, 1959, and concerns the association of hemadsorption virus type 2 (parainfluenza 1) and Asian influenza virus A with infectious croup. A diagnosis of virus infection could be assigned to 71 per cent of the children with croup. The associated viruses included influenza virus, hemadsorption virus types 1 and 2, croup-associated virus, and adenovirus types 1 and 5. In the study by these authors "the agents whose association with croup was best substantiated were hemadsorption virus type 2 and the virus of Asian influenza A." As the authors point out, the association of influenza viruses with croup was long suspected and is now being documented.[1, 11] The association of the hemadsorption virus type 2 with croup is a new observation, and according to the authors was the most striking finding in their investigations with the hemadsorption viruses. In all probability these new myxoviruses will be classified as *Myxovirus parainfluenzae* 3 (hemadsorption virus type 1) and *Myxovirus parainfluenzae* 1 (hemadsorption virus type 2).[12]

Significant bacterial pathogens were not found to be associated with these respiratory illnesses. An interesting clinical observation was the notable differences in the manifestations of this type of virus croup from those considered characteristic of the so-called supraglottic form of croup resulting from infection with *H. influenzae* type B. Another observation of interest concerned the predilection of type 2 hemadsorption virus for male children, a finding in accord with earlier notations that croup occurs less frequently in females. In a careful summary of the clinical and laboratory findings the authors state that if these studies ". . . are confirmed in the future, hemadsorption virus Type 2 is probably one of the major causes of infectious croup and accounts for a large segment of previously unexplained illness. These observations, if substantiated, will make this agent a leading candidate for inclusion in any vaccine against respiratory tract viruses."[10]

RUSSELL J. BLATTNER

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Correspondence

To the Editor:

I read with great interest the various references in the July issue of THE JOURNAL OF PEDIATRICS on Formula Sterilization. There was one feature about the use of hot domestic tap water which was not discussed. I refer to the possibility of toxic hazards from the use of hot tap water. My doubts were raised with and confirmed by our Division of Water Control and the Bureau of Sanitary Engineering of the New York City Department of Health. Some quotations from their report to me follow:

"The solution of various pipe metals such as zinc, copper, lead and iron is accelerated with the rise in temperature of the water. This is particularly severe for New York City's water supply which is soft and corrosive. It is a well known fact that hot water pipes have to be replaced much sooner than cold water pipes due to corrosion.

"The particles of corrosion are displaced from the pipe and settle at the bottom of the riser, on the bottom of horizontal piping and on the bottom of water tanks. Heavy drafts of water carry these loosened particles of corrosion to the tap.

"Zinc is removed from galvanized pipe, zinc and copper from brass pipe and copper, lead and iron go into solution from pipe of such materials. From brass pipe, the zinc is removed first. This causes the residual copper to become brittle and to scale off. Everyone is familiar with the blue and green copper stains on bathroom fixtures connected with brass or copper pipe due to a slow leak from the faucet.

"The constant heating and cooling of the hot water line causes the particles of corrosion to loosen and fall off and to expose new pipe surface for further corrosion. The cold water line is not subject to such severe action.

"The greater agitation of the water in hot water lines tends to keep the particles of corrosion in suspension to be drawn out at the tap.

"Because of the rapid clogging of hot water lines due to the very great expansion of the corroded pipe film, reversal of flow occurs which raises up the corrosive particles deposited on the bottom of horizontal piping.

"Laboratory examinations for lead have again and again shown quantities of lead in excess of the U. S. Public Health Service standards for water drawn from hot water taps while water in the same apartment drawn from cold water lines showed a quantity of lead well below the limit set by the standards.

". . . lead is found more than twice as often in samples collected in the same apartments on the hot water lines, and for significant differences of .03 ppm [parts per million] and greater, the ratio is 3 to 1.

"Four samples showed the same amount of lead for both the cold water and hot water lines.

"It was impossible in most cases to determine the composition of the complete piping system. Since deposits of calcium carbonate form more readily on hot water pipes than on the cold water lines, the hot water lines would more readily be replaced due to poor flow conditions. Because of the high cost of lead, no replacements with lead pipe have been made for many years. It is possible, therefore, that in some of the samples which showed greater lead for the cold water line that the hot water line to the same apartment contained less lead piping than the cold water line.

"We have in our files the report of an investigation of a case where several persons became ill due to excessive copper in the water drawn from the bottom of a hot water tank.

"The section of the Health Code which regulates the addition of chemicals to the water supply in buildings does not apply to the treatment of water for any use which does not include human consumption. This includes boiler water used only for space heating in buildings. Building superintendents, experienced and inexperienced, add a variety of chemicals including alkalies and chromates to boiler water for the inhibition of corrosion. Many of these chemicals are toxic. The hot water used for domestic purposes is often heated by a coil or coils of pipe immersed in such boiler water. A corroded hole in the domestic hot water line could cause some of this boiler water containing toxic chemicals to pass into the domestic line due to the greater pressure in the hot water boiler.

"The addition of certain chemicals to the water supply in buildings is permitted in our Health Code. This treatment is more often performed on domestic hot water lines than on the cold water lines. In a few cases, we have found excessive quantities of these chemicals in the water supply.

"The U. S. Public Health Service states that the following chemical substances should preferably not occur in excess of the following concentrations where other more suitable supplies are available:

Copper should not exceed 3.0 ppm (parts per million);

Iron and manganese together should not exceed 0.3 ppm;

Zinc should not exceed 15 ppm; and the presence of lead in excess of 0.1 ppm shall constitute grounds for rejection of the supply.

"*Summary.* Water drawn from hot water taps usually contains greater amounts of metallic substances than water drawn from cold water taps and in addition may contain alkalies and toxic chemicals legally intended only for water used for space heating. Because of the more prevalent chemical treatment of hot water systems for anti-corrosion purposes there exists the greater possibility of an occasional overdose of treatment in water drawn from the hot water tap."

It would appear that the slight convenience of using hot water from a tap does not therefore justify recommending its use when cold water is so readily available for heating, and while it is being heated, why not heat it to boiling?

Sincerely yours,

HAROLD JACOBZINER, M.D.
Assistant Commissioner
Maternal and Child Health
The City of New York Department of Health

Books

The Physiology of the Newborn Infant, ed. 3. Clement A. Smith, Springfield, Ill., 1959, Charles C Thomas, 485 pages. Price $12.50.

This book is so well established and accepted that only the announcement of a new edition is necessary. The pediatric world is again indebted to Clem Smith for assembling the large mass of experimental data on the fetus and newborn infant in a single volume and especially for the clinical interpretations which have made the book so meaningful to student and practitioner. This book should be standard equipment for anyone who is responsible for the medical care of the newborn infant. For the student who is being introduced to neonatal pediatrics, the book is invaluable.

Poisoning. A Guide to Clinical Diagnosis and Treatment, ed. 2. W. F. von Oettingen, M.D., Philadelphia, 1958, W. B. Saunders Co., 627 pages.

A second enlarged and revised edition of the Manual on poisoning by Dr. von Oettingen of the U. S. Public Health Service. Since the first edition six years ago, new types of poisoning have been reported, together with new methods of detection and treatment. A valuable book of reference.

Cerebral Palsy in Childhood. Grace E. Woods, M.D., Bristol, England, 1957, John Wright & Sons Ltd.

Cerebral palsied children were referred to the Cerebral Palsy Assessment Clinic in Bristol for evaluation as to proper placement for education or training. This book is a review of over 300 patients seen in the Clinic. Two-thirds of the book is devoted to discussion of the major clinical types, each subdivided by etiology. There follows a brief discussion of mentality, visual and speech defects, sensory defects, convulsions, and assessment of educability. There is no discussion of prognosis, self-care ability, or therapy. The statistics are not clear.

This book is of limited general interest, but will serve as a diagnostic reference.

News and Notes

The **Ninth Annual Postgraduate Seminar for Pediatricians** will be conducted at St. Christopher's Hospital for Children, the Pediatric Department of Temple University School of Medicine, Philadelphia, June 1 to 4, 1960. Half-day sessions will be devoted to various phases of pediatric medicine.

For information regarding enrollment, program, registration fee, etc., write to Dr. John B. Bartram, St. Christopher's Hospital for Children, 2600 North Lawrence Street, Philadelphia 33, Pennsylvania.

The **American College of Allergists Graduate Instructional Course and Annual Congress** is scheduled for February 28—March 4, 1960, at The Americana Hotel, Bal Harbour, Miami Beach, Florida. For information contact John D. Gillaspie, M.D., Treasurer, 2049 Broadway, Boulder, Colorado.

Officers for 1959-1960 of the Pediatric Section of the **Medical Society of the County of Kings**, New York, are President, Abraham Gilner; Vice-president, Saul Starr; Secretary, Ben M. Zweifler; and Treasurer, Ernest Heffer.

The **New York Eye and Ear Infirmary's alumni association's annual spring meeting** will be April 4-7, 1960, at the Infirmary. The theme of the meeting will be pediatric ophthalmology and otolaryngology with an EENT symposium on "Nystagmus as a Pediatric Problem" and closed-circuit television demonstrations of surgical procedures.

Other symposia will be on occular complications attending infectious diseases of childhood, surgical correction of congenital deformities of the eye and adnexa, glaucoma and cataracts in pediatrics, office management of the pediatric eye patient, diagnosis and rehabilitation of hearing problems in children, and ankylosis of the stapes.

For information write to Dr. John R. Finlay, Secretary, Alumni Association, 218 Second Avenue, New York 3, New York.

A number of **Fellowships in Pediatric Endocrinology** are available at salaries of $5,000 to $5,500 per year. Such trainees must have completed residencies of two to four years on pediatric house staffs and, preferably, should be interested in academic or research careers. They will be accepted for periods of one or two years' training in pediatric endocrinology. One year will be spent largely in clinical diagnostic and investigative work and the other in laboratory research.

Those interested and qualified may write to Dr. Lawson Wilkins, The Harriet Lane Home, Johns Hopkins Hospital, Baltimore 5, Maryland, sending *curriculum vitae* and letters of recommendation.

Editor's Column

ETIOLOGY OF ALLERGIC DISEASES

In the last few years immunologic research has produced convincing evidence that the patient's own immune mechanism is a causative factor in several important diseases of obscure etiology, e.g., Hashimoto's disease, lupus erythematosus, the demyelinating diseases, periarteritis nodosa, glomerulonephritis, and rheumatoid arthritis. Therefore these diseases must be considered immunologic disorders. In contrast to the classical hypersensitivity reactions such as ragweed pollinosis, anaphylaxis, and serum disease, where the offending antigen comes from outside the host, the above-mentioned diseases are known (or thought) to be characterized by the production of antibodies that combine with some normal or modified tissue component such as nucleoprotein (lupus), thyroid (Hashimoto's disease) or myelin. Thus the term "autoimmune disease" has been added to our immunologic vocabulary.

The existence of autoimmune reactions has been suspected for a long time but an understanding of why and how they occur had to await the development of adequate immunohistochemical techniques. With the impetus provided by investigators such as Heidelberger, Kabat, Dan Campbell, Coons, and Pressman—to name but a few—the era of immunohistochemistry came into being and produced such useful tools as fluorescent and isotopic tagging of antibody. With the techniques now available for separating antibodies[1] and tissue antigens from infectious particles,[2] one can safely predict rapid progress in our knowledge of the perplexing variety of immunologic reactions man is heir to.

Despite these technical accomplishments, however, some of the most basic and fundamental questions in immunology remain unanswered. For example, "How is antibody produced?" At the present time the generally accepted template theory is being challenged by the clonal selection theory of Burnet,[3] the natural selection concept of Talmage,[4] and the genetic elective modification by Lederberg.[5] Theories have very little value, however, without experimental evidence. And in this connection the ingenious experiments whereby Nossal and Lederberg[6] showed that antibody-producing tissue cells may be monospecific, viz., make only one type of antibody, not only support the Lederberg concept but they may also lead us to understand where peculiar antibodies such as atopic reagin, delayed reaction antibody, and rheumatoid factor come from. For it is now known through the brilliant work of Pappenheimer[7]

and others[8, 9] that an antigenic stimulus—even by a highly purified substance—results not in a single antibody but a family of antibodies with a whole spectrum of physical characteristics, specificities, and avidities for combining with antigen.

The investigations mentioned so far deal more with the question, "How is antibody produced?" than with the more important one, "Why do certain human beings make antibodies against bland substances like ragweed pollen, penicillin, and, worst of all, their own tissues?" Such molecules must be "foreign" to the host, but how can one's own tissues be foreign? This is precisely the question Najjar and Robinson answer to their satisfaction by the unified concept they briefly outline in this issue. It is based on experimental findings which in some instances may be open to more than one interpretation, but it offers a reasonable explanation for most, if not all, allergic phenomena, and it is particularly promising as a mechanism for autoimmune disorders. It is also a challenging concept which undoubtedly is shaping current research.

None of the discoveries or concepts referred to in this editorial has produced any information that can now be used to reduce the incidence or improve the management of any of the allergic diseases. Yet they hold great promise for clinicians because they indicate the intensity with which immunologic research is being pursued, especially in the area of autoimmune reactions. Nothing like a major breakthrough has occurred yet, but it could happen soon. If it does, important clinical applications will certainly follow.

EARLE H. SPAULDING, PH.D.

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EVALUATION OF GROWTH DATA

The article by Dreizen and associates provides interesting new evidence of the interrelationships between season, growth, calcification of bone centers, and chronic undernutrition. The findings are in some respects in accord with earlier reports of seasonal differences, based on studies of supposedly normal children. The references to the latter are in general agreement that the peak of first appearance of osseous centers and the maximum rate of growth in body length occur in the spring. The season of maximum gain in weight, however, appears to be autumn.

In the study being reported it was found that malnourished children tend to be far behind normal children in the age of appearance of osseous centers generally and that they reach their seasonal peak of maximum appearance in the summer months (June through August), which is about 3 months later than has been found for other children. The delay in appearance of the carpals is greater than that of the metacarpals and phalanges, but this is understandable since the latter normally appear at later ages. Progress in most aspects of development is more readily retarded in the young or very immature individual than in the older child.

The authors have used the Wetzel Grid to obtain a single measure of the "rate of general body growth." This method of assessing the rate of growth of these children seems unfortunate because the curve revealed on the grid provides a ratio of weight to height. This ratio shows that for the group of malnourished children the slowest rate of growth occurred most commonly during the months June through August. In this season normal children elsewhere have been found to be growing most rapidly in height but gaining least in weight. Although rate of gain in weight is a function of general rate of growth, it reflects also accumulations or loss of subcutaneous fat. It would seem particularly important in this study to keep rates of gain in height and in weight separate. Under the circumstances the actual significance of the seasonal differences in the growth of these children from that of other groups cannot be assessed.

The authors conclude their report with the suggestion that "the temporal coincidence of a peak in occurrence of new ossification centers and a diminution of rate in general body growth may be related to a seasonal variation in the availability and utilization of specific nutrients and accessory food factors."

The fact that reports from several countries, based upon normal as well as undernourished children, agree that there are seasonal differences in rates of growth in height and of gain in weight and in frequency of appearance of new osseous centers in radiographs makes it appear hazardous to suggest that these seasonal variations can all be explained by seasonal differences in the availability or utilization of specific nutrients or even general dietary considerations. In fact, the finding of a difference of three months in the timing of the peak of new centers between the group studied by Reynolds and Sontag in Ohio, reported in 1944, and the Alabama Study just being reported hardly

seems to justify the conclusion that undernutrition alters the characteristic seasonal pattern associated with the emergence of ossification centers. There would seem to be possibilities for other unknown variables to exist between these groups. The findings do justify the hypothesis, however, that undernutrition tends to delay the laying down of calcium in bone centers. This is in substantial agreement with other reports of the effects of undernutrition on this process.

It should be pointed out that there are many environmental factors which change with season and may account, in part at least, for seasonal differences in the progress of growth and development. In the infant, excessive heat or humidity tends to affect food intake, fluid balance, digestive and probably metabolic processes, the incidence of gastrointestinal upsets, sleep, and activity. These factors would be expected to have the greatest effect on weight, diminishing average gains in spring or summer and leading to more rapid gains in the autumn. In older children the summer season, in contrast to that of winter, brings about striking changes in habits and physical activities, as well as in dietary intake. The incidence of illnesses, as well as differences in their types and severity, may well be factors in leading to changes in rates of progress. In this connection some attention might well be given to the possibility of a time lag between the first appearance of a factor which has the potentiality for modifying the rate of growth or skeletal maturation and the time at which these effects become manifest.

The attempt in the present study to identify relationships between nutrition and rate of growth or skeletal maturation is to be commended. The purpose in this comment is only to call attention to the complexity of the problems involved. There is need for more comprehensive knowledge of the changes with season in all environmental factors which may affect individuals. With more comprehensive histories in hand one might separate out those children in the group who manifest the maximum of seasonal differences in rate of growth and maturation and contrast them with those who show a minimum of such differences. One could then study these two groups separately from the standpoint of differences in the nature and extent of recorded environmental factors of potential significance.

HAROLD C. STUART, M.D.

NINTH INTERNATIONAL PEDIATRIC CONGRESS

The Ninth International Pediatric Congress at Montreal, Canada, July 19 to 25, 1959, was an outstanding success and in every way lived up to expectations. It would be difficult to conceive that a meeting of such size could be conducted more efficiently, more effectively, and apparently so effortlessly. It was a brilliant example of meticulous, intelligent planning. The 1,600 pediatricians from more than 50 countries are deeply indebted to the Canadian group.

There were three reasons, in particular, for the success of the meeting: First, a splendid scientific program had been arranged on topics of current interest with participants from all parts of the world who have been responsible for the recent advances in pediatrics; attendance was excellent and in the smaller sessions there were ample opportunities for discussion. Second, the physical setup at the recently opened Queen Elizabeth Hotel is especially adapted for a meeting requiring six or seven simultaneously conducted sessions, all within juxtaposition, so that one could move easily from one meeting room to another, making it possible to select specific papers in each; the large exhibit room was on the same floor. Third, Montreal is an interesting city and the host, the *Canadian Paediatric Society—Société Canadienne de Pédiatrie,* had planned delightful entertainment including two excursions with buffet suppers and a concert by the Montreal Symphony Orchestra.

The Prime Minister of Canada, the Honorable John G. Diefenbaker, gave the welcoming address at the opening meeting of the Congress which was under the patronage of Her Majesty, Queen Elizabeth.

Summaries of the various plenary sessions which were presented on the final afternoon provided valuable perspectives of the meetings which one was unable to attend.

What was most obvious to all present was the effective work of the various Congress committees. It was clear that they had been toiling for months on the various tasks assigned them, with the result that everything moved without a hitch or confusion. We are happy to be able to present a picture of three of the men to whom much of the credit for the success of the meeting must be given: Dr. Alan Ross of Montreal, President; Dr. R. L. Denton of Montreal, Secretary-General; and Dr. J. Harry Ebbs of Toronto, Chairman of the Scientific Program Committee. We thank and salute them.

Lisbon, Portugal, was selected for the Tenth Congress in 1962.

Denton **Ross** **Ebbs**

From an Unofficial Session

Achar
India

Clifford
U. S. A.

Kerpel-Fronius
Hungary

Nelson
U. S. A.

Ahvenainen
Finland

H. Bakwin
U. S. A.

I. Chaudhuri
K. C. Chaudhuri
India

Farber
U. S. A.

Gaisford
England

Bickel
Germany

Clement Smith
U. S. A.

Carl Smith
U. S. A.

Zetterström
Sweden

Veeder
U. S. A.

Heymann
South Africa

R. Bakwin
U. S. A.

Dr. and Mrs. Hamid Ali Khan
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Viral gastroenteritis **just has to run its course. But there *is* something you can now do about one of its most debilitating symptoms — vomiting. Take, for example, the case of a one-year-old baby boy, who developed acute viral gastroenteritis with vomiting every 15 minutes for two-and-a-half hours. *Tigan* was given in suppository form, repeated after four hours. "Onset of relief in one half hour and no recurrence of symptoms and no side effects except that he slept two hours after first suppository."***

to prevent and stop nausea and vomiting

new Tigan PEDIATRIC SUPPOSITORIES

safe—no special precautions, no known contraindications

Dosage **(q.i.d. or as directed): Children over 90 lbs, 1 suppository; 30 to 90 lbs, ½ to 1 suppository; under 30 lbs, ½ suppository. *Supplied:* Tigan Pediatric Suppositories – 200 mg, boxes of 6.**

*L.A. McLaughlin, Colloquium on the Pharmacological and Clinical Aspects of Tigan, New York, May 15, 1959.

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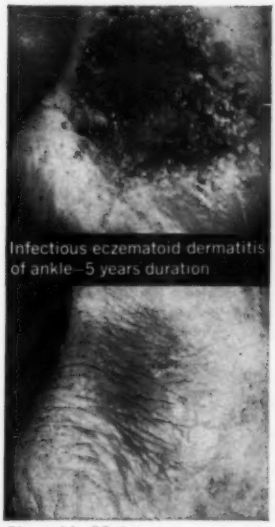

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References: 1. Shelmire, J.B., Jr.: Monographs on Therapy 3:164 (Nov.) 1958. • 2. Nix, T.E., Jr., and Derbes, V.J.: Monographs on Therapy 3:123 (Nov.) 1958. • 3. Robinson, R.C.V.: Bull. School of Med., U. Maryland 43:54 (July) 1958. • 4. Sternberg, T.H.; Newcomer, V.D., and Reisner, R.M.: Monographs on Therapy 3:115 (Nov.) 1958. • 5. Clark, R.F., and Hallett, J.J.: Monographs on Therapy, 3:153 (Nov.) 1958. • 6. Smith J.G., Jr.; Zawisza, R.J., and Blank, H.: Monographs on Therapy, 3:111 (Nov.) 1958. • 7. Monographs on Therapy, 3:137 (Nov.) 1958. • 8. Howell, C.M., Jr.: North Carolina M.J. 19:449 (Oct.) 1958. • 9. Bereston, E.S.: South. M.J. 50:547 (April) 1957.

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1. A.M.A. Committee on Toxicology: Accidental Iron Poisoning in Children, J.A.M.A. 170:676, June 6, 1959.
2. Franklin, M., et al.: Chelate Iron Therapy, J.A.M.A. 166:1685, Apr. 5, 1958.

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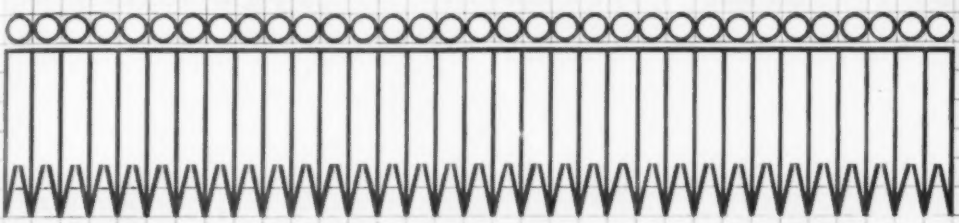

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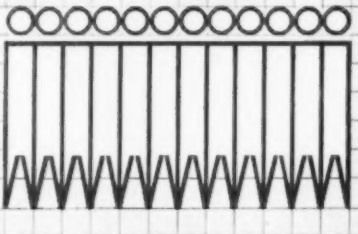

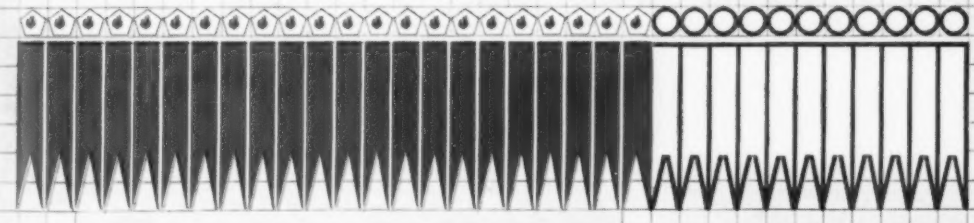

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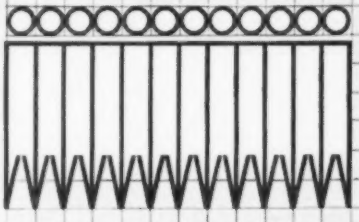

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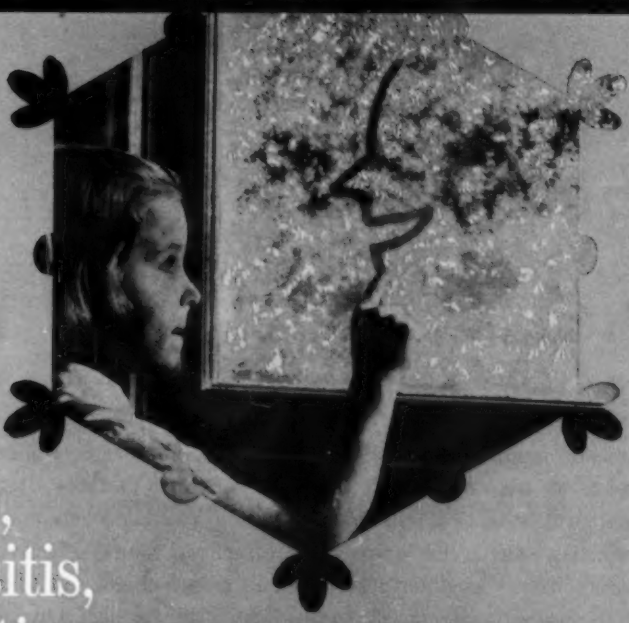

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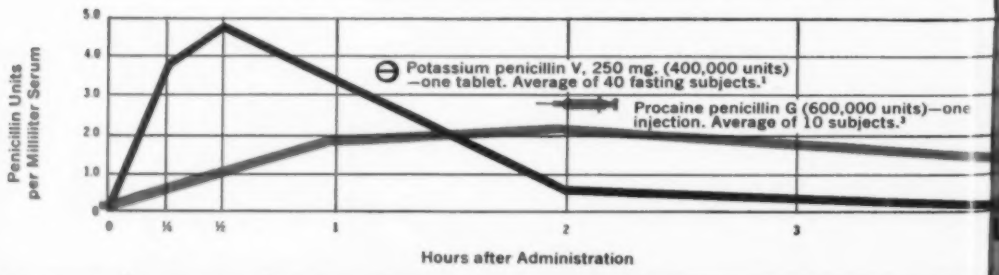

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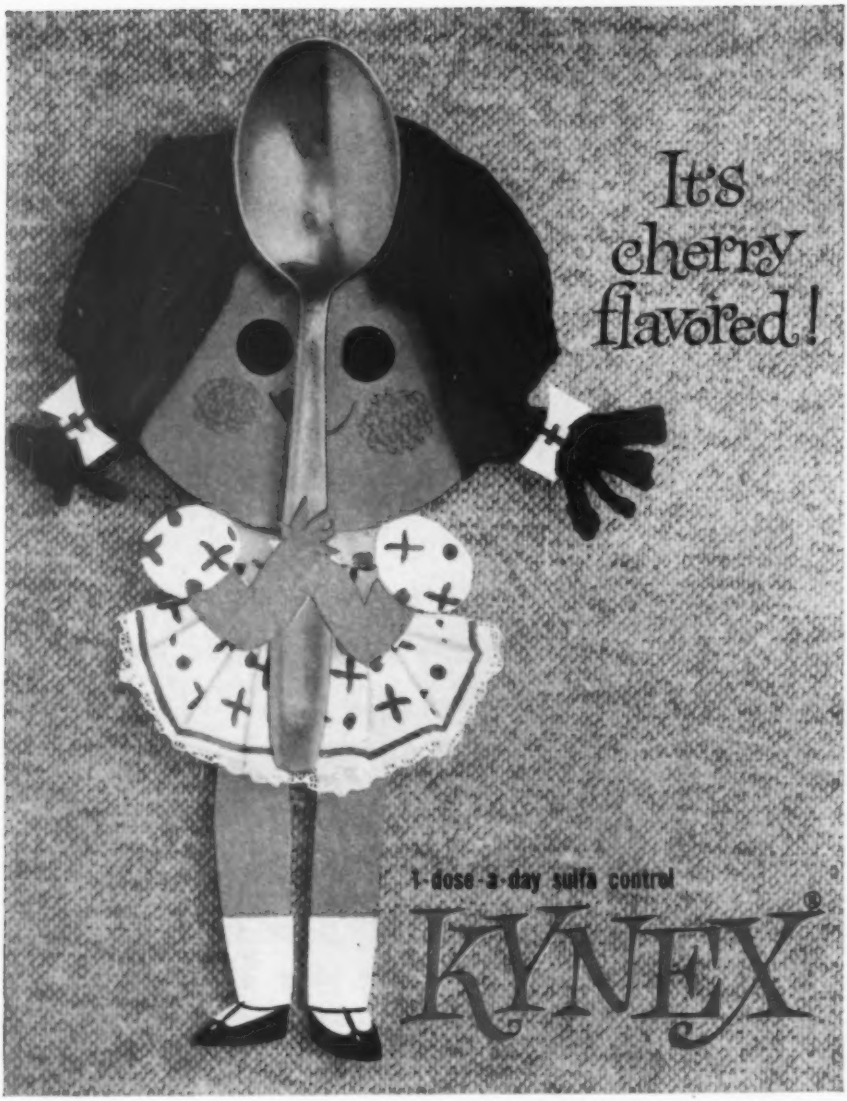

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N¹ Acetyl Sulfamethoxypyridazine

Recommended dosage: First-day dose is 1 teaspoonful (250 mg.) for each 20 lbs. body weight up to 80 lbs. For each day thereafter, ½ teaspoonful for each 20 lbs. For 80 lbs. and over use adult dosage of 4 teaspoonfuls (1.0 Gm.) initially, and 2 teaspoonfuls (0.5 Gm.) daily thereafter. Administer after a meal.

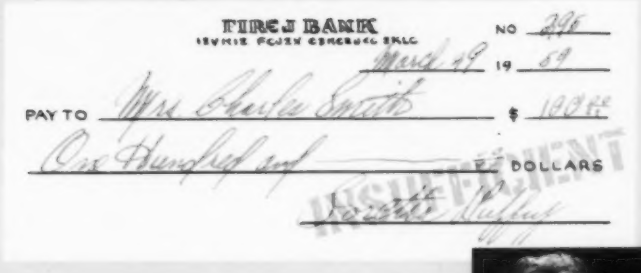
Supplied: Each teaspoonful (5 cc.) contains 250 mg. of sulfa-methoxypyridazine activity. Bottles of 4 and 16 fl. oz.

LEDERLE LABORATORIES Lederle

A Division of AMERICAN CYANAMID COMPANY, Pearl River, N. Y.

women of childbearing age... and growing children... may be

OVERDRAWN AT THE BLOOD BANK



Women of menstrual age and growing children have higher iron requirements than other individuals. Hence iron-deficiency anemias occur most often in these groups. Many clinicians recognize that most women need a hematinic for six weeks each year during reproductive years.

Livitamin, with peptonized iron and B complex, offers an excellent formula to restore depleted iron reserves in both adults and children. Peptonized iron is well absorbed and stored, and better tolerated than ferrous sulfate. B complex and other factors provide nutritional support.

LIVITAMIN®

with Peptonized Iron

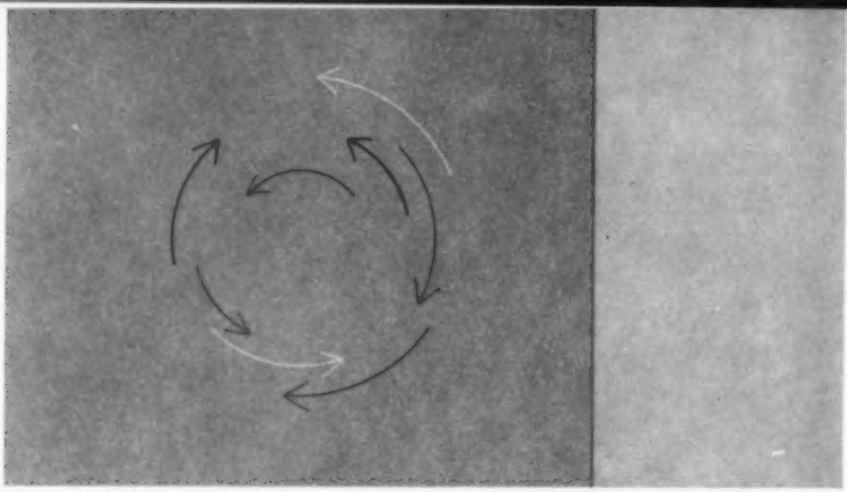
FORMULA: Each fluidounce contains:

Iron peptonized (Equiv. in elemental iron to 71 mg.)	420 mg.
Manganese citrate, soluble	158 mg.
Thiamine hydrochloride	10 mg.
Riboflavin	10 mg.
Vitamin B_{12} Activity (Derived from Cobalamin conc.)	20 mcg.
Nicotinamide	50 mg.
Pyridoxine hydrochloride	1 mg.
Pantothenic acid	5 mg.
Liver fraction 1	2 Gm.
Rice bran extract	1 Gm.
Inositol	30 mg.
Choline	60 mg.

SUPPLIED IN LIQUID OR CAPSULE.

The S.E. MASSENGILL Company

BRISTOL, TENNESSEE • NEW YORK • KANSAS CITY • SAN FRANCISCO



Livitamin assures patient acceptance because it is highly palatable. Peptonized iron provides a virtually predigested form of iron. Recent studies* show peptonized iron has these advantages:

- Rapid response in iron-deficiency anemias
- Non-astringent
- Absorbed as well as ferrous sulfate
- Better gastric toleration than ferrous sulfate
- Less constipating than ferrous sulfate

LIVITAMIN®

with Peptonized Iron

...the preferred hematinic

*Keith, J.H.: Utilization and Toxicity of Peptonized Iron and Ferrous Sulfate, Am. J. Clin. Nutrition 1:35 (Jan.-Feb., 1957).

The S. E. MASSENGILL Company BRISTOL, TENNESSEE

NEW YORK • KANSAS CITY • SAN FRANCISO

Fostex®
treats their acne while they wash

degreases the skin helps remove blackheads dries and peels the skin

...and this is how it works

Fostex provides essential actions necessary in treating acne. It washes off excess oil. It unblocks pores by penetrating and softening blackheads. It dries and peels the skin, removing papule coverings, thus permitting drainage of sebaceous glands.

Fostex contains Sebulytic®,* a combination of surface-active wetting agents with remarkable antiseborrheic, keratolytic and antibacterial actions . . . enhanced by sulfur 2%, salicylic acid 2%, hexachlorophene 1%.

*sodium lauryl sulfoacetate, sodium alkyl aryl polyether sulfonate and sodium dioctyl sulfosuccinate.

Your patients will like Fostex because it is so simple to use. They simply wash acne skin 2 to 4 times a day with Fostex, instead of using soap.

FOSTEX CREAM

. . . in 4.5 oz. jars. For therapeutic washing in the initial phase of oily acne treatment.

Write for samples.

FOSTEX CAKE

. . . in bar form. For therapeutic washing to keep the skin dry and free of blackheads during maintenance therapy. Also used in relatively less oily acne.

WESTWOOD PHARMACEUTICALS Buffalo 13, New York

LEDERLE INTRODUCES...

a masterpiece

greater antibiotic activity

Milligram for Milligram, DECLOMYCIN exhibits 2 to 4 times the activity of tetracycline against susceptible organisms. (*Activity* level is the basis of comparison—not quantitative blood levels—since action upon pathogens is the ultimate value.*) Provides significantly higher serum activity level . . .

with far less antibiotic intake

DECLOMYCIN demonstrates the highest ratio of prolonged activity level to daily milligram intake of any known broad-spectrum antibiotic. Reduction of antibiotic intake reduces likelihood of adverse effect on intestinal mucosa or interaction with contents.

unrelenting peak antimicrobial attack

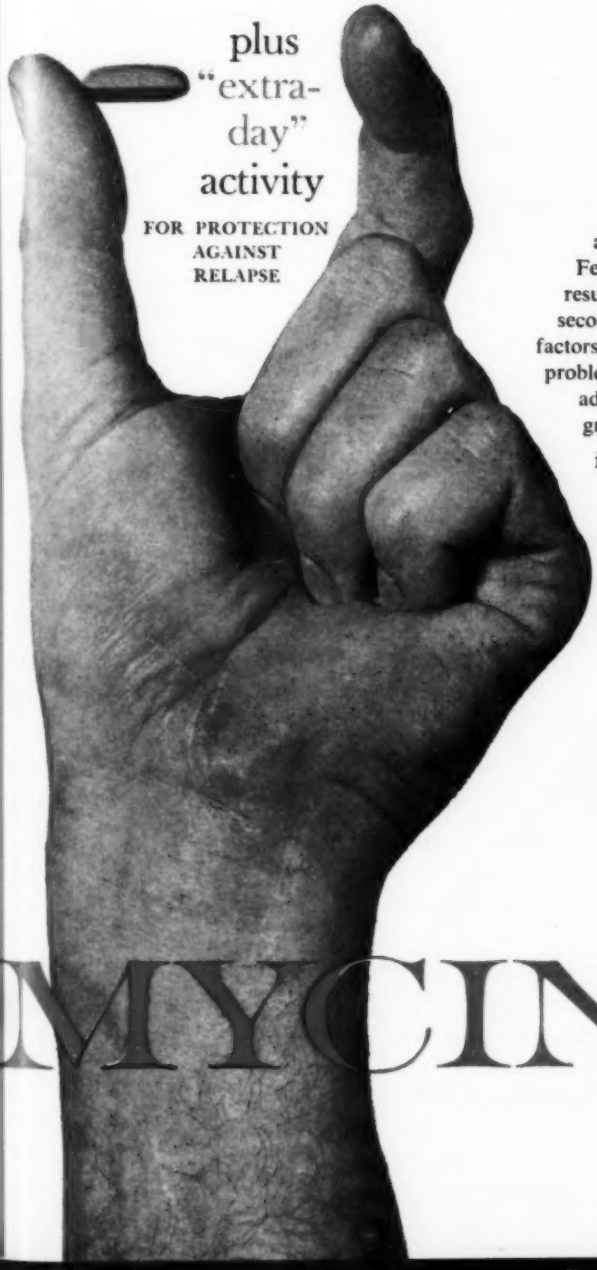
The DECLOMYCIN high activity level is uniquely constant throughout therapy. Eliminates peak-and-valley fluctuation, favoring continuous suppression. Achieved through remarkably greater stability in body fluids, resistance to degradation and a low rate of renal clearance.

*Hirsch, H. A., and Finland, M.: *New England J. Med.* 260:1099 (May 28) 1959.

DECLO

Demethylchlortetracycline Lederle

# of antibiotic design



plus "extra-day" activity

FOR PROTECTION AGAINST RELAPSE

DECLOMYCIN maintains activity for one to two days after discontinuance of dosage. Features unusual security against resurgence of primary infection or secondary bacterial invasion—two factors often resembling a "resistance problem"—enhancing the traditional advantages of tetracycline... for greater physician-patient benefit

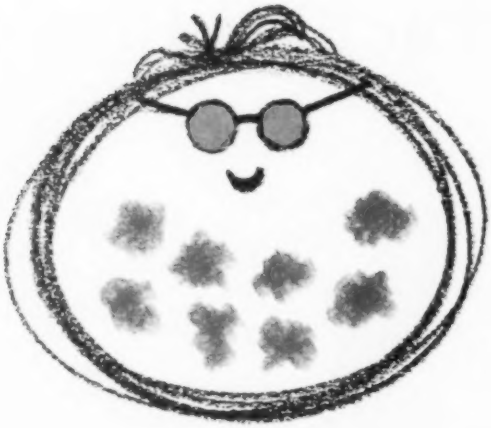
in the distinctive, dry-filled, duotone capsule

immediately available as:
DECLOMYCIN
Capsules, 150 mg.,
bottles of 16 and 100.
Adult dosage: 1 capsule
four times daily.

MYCIN®

Lederle

LEDERLE LABORATORIES
a Division of
AMERICAN CYANAMID COMPANY
Pearl River, New York



FOR PREVENTION OR MODIFICATION OF

MEASLES

SPECIFY

GAMULIN*

Passive immunity to measles, for at least three weeks, is usually provided by a preventive dose of Gamulin (0.1 cc. per pound body weight) administered within six days after exposure. A smaller dose (0.02 cc. per pound) modifies the attack of measles—shortens the duration of acute illness and tends to prevent complications such as pneumonia, otitis media, and encephalitis.

Specify Gamulin for measles prophylaxis and for any other condition in which gamma globulin is indicated: prevention or modification of infectious hepatitis and poliomyelitis, as well as therapy in conditions related to serum gamma globulin deficiency.

In Gamulin, the major antibody-containing fraction of plasma is separated from other proteins by critically-controlled procedures which result in a gamma globulin concentration approximately 25 times that of normal human plasma.

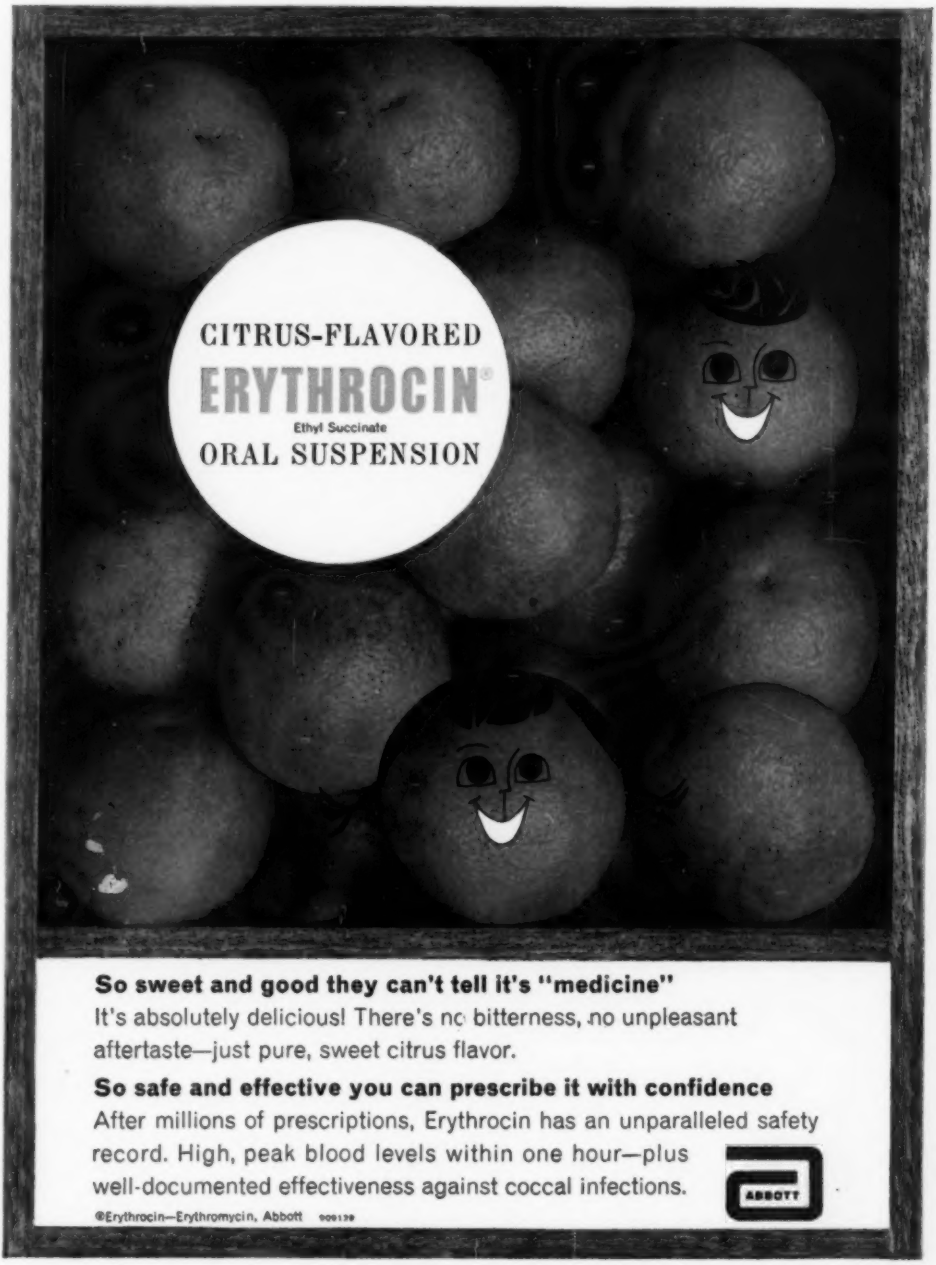
Gamulin is supplied in 2 cc. and 10 cc. vials.

PITMAN-MOORE COMPANY

a leader in biological research and one of the world's major producers of biologicals

*Trademark for Poliomyelitis Immune Globulin (PM CO. Bio. 172)

no turned-up noses at this new Erythrocin Suspension



So sweet and good they can't tell it's "medicine"
It's absolutely delicious! There's no bitterness, no unpleasant aftertaste—just pure, sweet citrus flavor.

So safe and effective you can prescribe it with confidence
After millions of prescriptions, Erythrocin has an unparalleled safety record. High, peak blood levels within one hour—plus well-documented effectiveness against coccal infections.

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now! liquid tetracycline in premeasured doses

hold here

tear

and press

Squibb first in pediatrics

Sumycin pressules

osphate Potentiated Tetracycline Aqueous Drops

SUMYCIN® AND PRESSULES® ARE SQUIBB TRADEMARKS

for the mother . . CONVENIENT to give . . one can be . . baby gets all of the dose you prescribe.

for the child . . EASY to take . . the patient may be too young . . but Sumycin Pressules are delicious.

for the physician . . SIMPLE to prescribe . . the only premeasured . . tetracycline for oral use . . no leftover doses . . no . . doses . . economical . . prescribe just the amount needed. Each Sumycin Pressule delivers 1 cc. of an aqueous . . tetracycline suspension, potentiated with potassium metaphosphate, deliciously flavored with mixed fruits. This dose provides 100 mg. of tetracycline (HCl equivalent). DOSAGE: Just one Pressule q.i.d. for an average 1 to 5 year old. Infants and children should receive 10 to 20 mg. of tetracycline/lb. of body weight. Thus for a child weighing from 20 to 40 pounds, one Pressule q.i.d. will be sufficient for the vast majority of infections. For children weighing more than 40 pounds, give 2 or more Sumycin Pressules q.i.d., according to body weight, or Sumycin Syrup. For infants under 20 pounds, administer Sumycin Aqueous Drops. SUPPLIED: Sumycin Syrup, a fruit flavored aqueous suspension, buffered with potassium metaphosphate, containing tetracycline equivalent to 125 mg. tetracycline HCl per 5 cc., and Sumycin Aqueous Drops, a fruit flavored aqueous suspension, buffered with potassium metaphosphate, containing tetracycline equivalent to 100 mg. tetracycline HCl per cc.

SQUIBB

Squibb Quality – the Priceless Ingredient

SUMYCIN® AND PRESSULES® ARE BRANDS OF

WHEN THE BABY HAS COLIC "...AND

SCREAMS

WITH THE OUTRAGED VIGOR OF A WOUNDED TIGER AND PUNCTUATES HIS SHRIEKS WITH FLATUS..."*

Skopyl®

Methyl Scopolamine Nitrate

FOR THE TREATMENT OF INFANT COLIC

Easy Administration: Just **one** or **two** drops of Skopyl under the tongue, 20-30 minutes before each feeding — or 3 drops for an acute attack of colic.

Fast Action: The rapid absorption of Skopyl into the blood stream via the oral or sublingual route often gives immediate and dramatic relief of acute abdominal pain characteristic of infant colic.

Action and Safety: The main effect of Skopyl is peripheral. It has a particularly depressant effect on the tonus and motility of smooth musculature of the gastrointestinal tract. Because of Skopyl's high degree of selective action and favorable therapeutic index, the recommended small volume dose can generally be given with a minimum incidence of side effects.

*Editorial: New England J. Med. 260:246 (Jan. 29) 1959

Precautions: Fluid balance should be restored in dehydrated infants or those with oliguria before beginning treatment with Skopyl. **Indications:** Colic (paroxysmal fussing, infantile dyspepsia, irritable crying), infantile vomiting, infantile diarrhea, pyloric spasm. **Available:** 5 cc. dropper bottle. One drop=0.6 mg.; 40 drops=1 cc. **Pharmacia Laboratories, Inc.,** 501 Fifth Avenue, New York 17, N.Y.

Now 2 ways to specify Carnation Evaporated Milk infant formula

1 NEW! CARNALAC

...when maximum convenience is desired. New Carnalac is Carnation Evaporated Milk with carbohydrate and Vitamin D added. Diluted 1:1, it provides the typical Carnation Evaporated Milk formula as usually prepared at home.

2 CARNATION EVAPORATED MILK

...when maximum formula flexibility is desirable for the baby... or when maximum economy is necessary for young parents.

STRAIGHT LAST

REGULAR

ARCH FEATURE

MISMATES

You'll find everything you want and need in

Child Life SHOES

a complete line

Here are shoes for children that adapt themselves readily to your corrective prescriptions . . . yet every shoe is styled to look like a "regular" shoe . . . freeing your patients from any inferiority complex that might develop from having to wear shoes that are "different" in appearance from those worn by other children.

For over 35 years the makers of CHILD LIFE shoes have concentrated exclusively on juvenile footwear . . . making only quality shoes of leather for both "regular" wear and orthopedic service. Nine chances out of ten there is a specially selected CHILD LIFE dealer in your community who will be glad to accept your prescription work and who is competent to handle your instructions. Write for his name, and for the CHILD LIFE service booklet for the professional man, featuring representative shoes and wedging procedures.

HERBST Shoe Manufacturing Company
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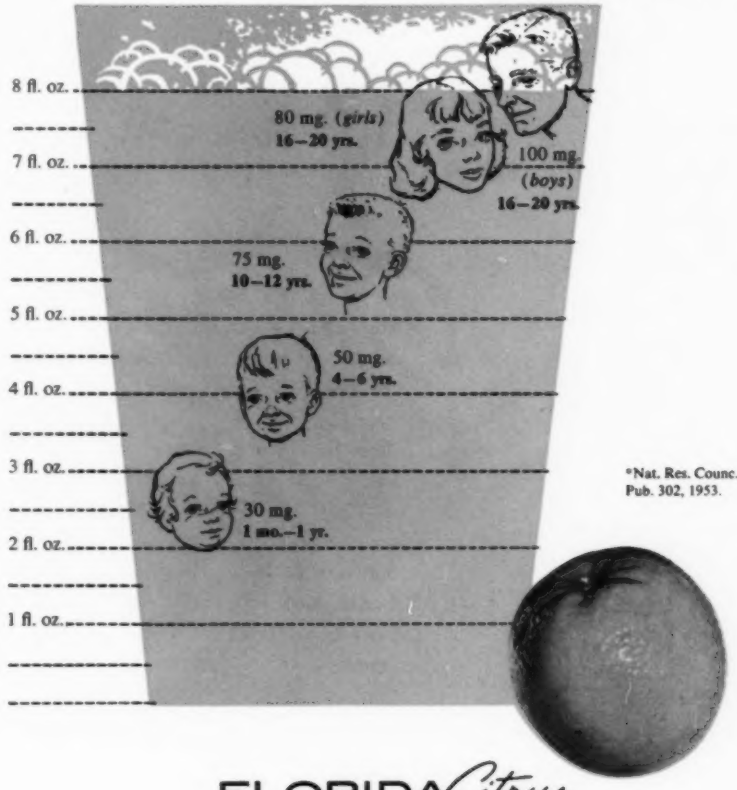
for developmental years
orange juice
capably supplies
recommended daily
intakes of vitamin C*



*Nat. Res. Counc., Pub. 302, 1953.

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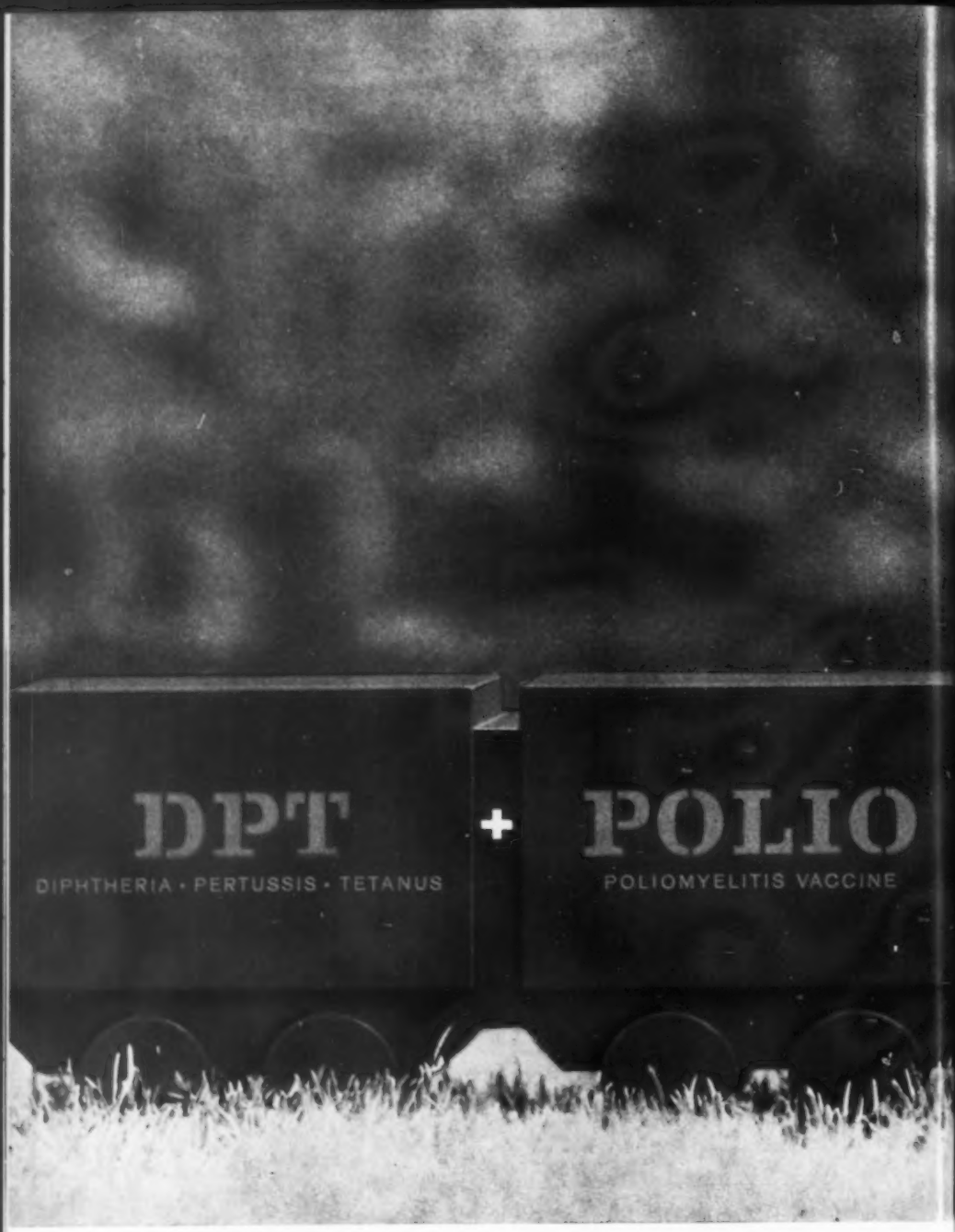
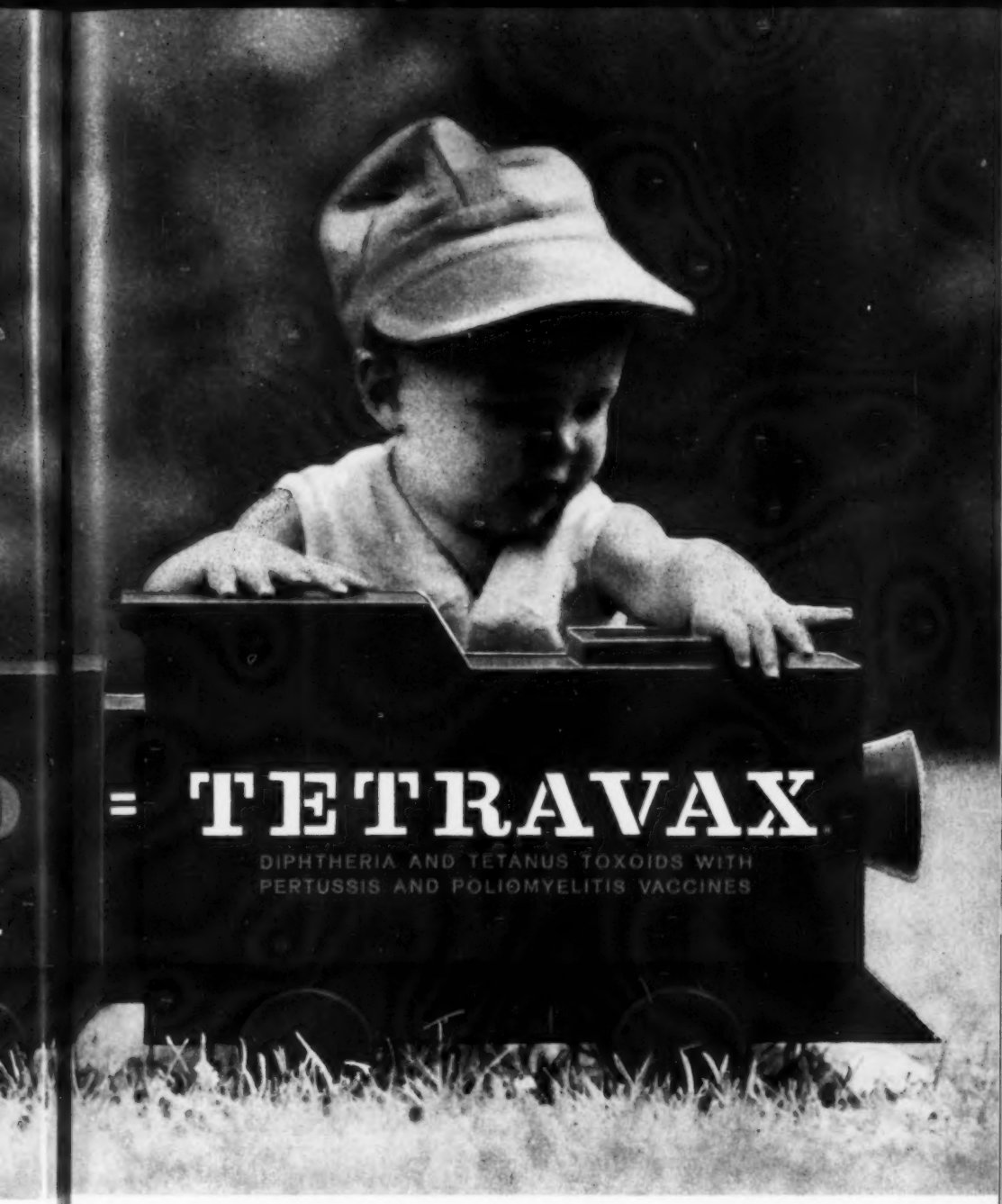
COMMISSION • LAKELAND, FLORIDA
ORANGES • GRAPEFRUIT • TANGERINES



FOR SIMULTANEOUS IMMUNIZATION

against 4 diseases:

Poliomyelitis – Diphtheria – Pertussis – Tetanus



now immunization is possible against more *diseases – with* fewer *injections*

Dosage: 1 cc. ***Supplied:*** 9 cc. vials in *clear plastic* cartons. Package circular and material in vial can be examined without damaging carton. Expiration date is on vial for checking even if carton is discarded.

MERCK SHARP & DOHME, DIVISION OF MERCK & CO., INC., PHILADELPHIA 1, PA.

TETRAVAX IS A TRADEMARK OF MERCK & CO., INC.

WHY ORANGE?

PALADAC®

liquid multivitamin supplement

is orange in color, aroma, and flavor because orange has specific meaning for children. From the time they first taste orange juice and later learn to enjoy orange-flavored drinks, orange ice, and orange candy, orange is a universal favorite—appealing, palatable, highly acceptable.

PALADAC is a balanced 9-vitamin formula that is even flowing, readily miscible, if desired, with milk, fruit juice, or other foods, and is stable, requiring no refrigeration.

Available in 4-ounce and 16-ounce bottles.

PARKE, DAVIS & COMPANY
DETROIT 32, MICHIGAN

PROTECT Little Braves' Scalps

CRADOL is an antibacterial penetrating emulsion with Diaparene®Chloride (methylbenzethonium chloride) in an oxycholesterin absorption base of liquid petrolatum and lanolin. The absence of keratolytic agents renders it safe to use for the prevention and treatment of cradle cap.*

Pasachoff, H. D. and Maffia, A. J., "A New Treatment for Cradle Cap", N. Y. State Med., 57:265-267, Jan. 15, 1957.

HOMEMAKERS PRODUCTS DIVISION
George A. Breon & Company
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ANOTHER FINE PEDIATRIC SPECIALTY BY BREON

BAKER'S MODIFIED MILK

HELPS PREVENT IRON DEFICIENCY ANEMIA

Iron deficiency anemia in infants continues to be a major health problem. Many factors can lower the infant's iron store at birth. Iron is supplied in Baker's Modified Milk to help prevent development of iron deficiency anemia in later infancy.

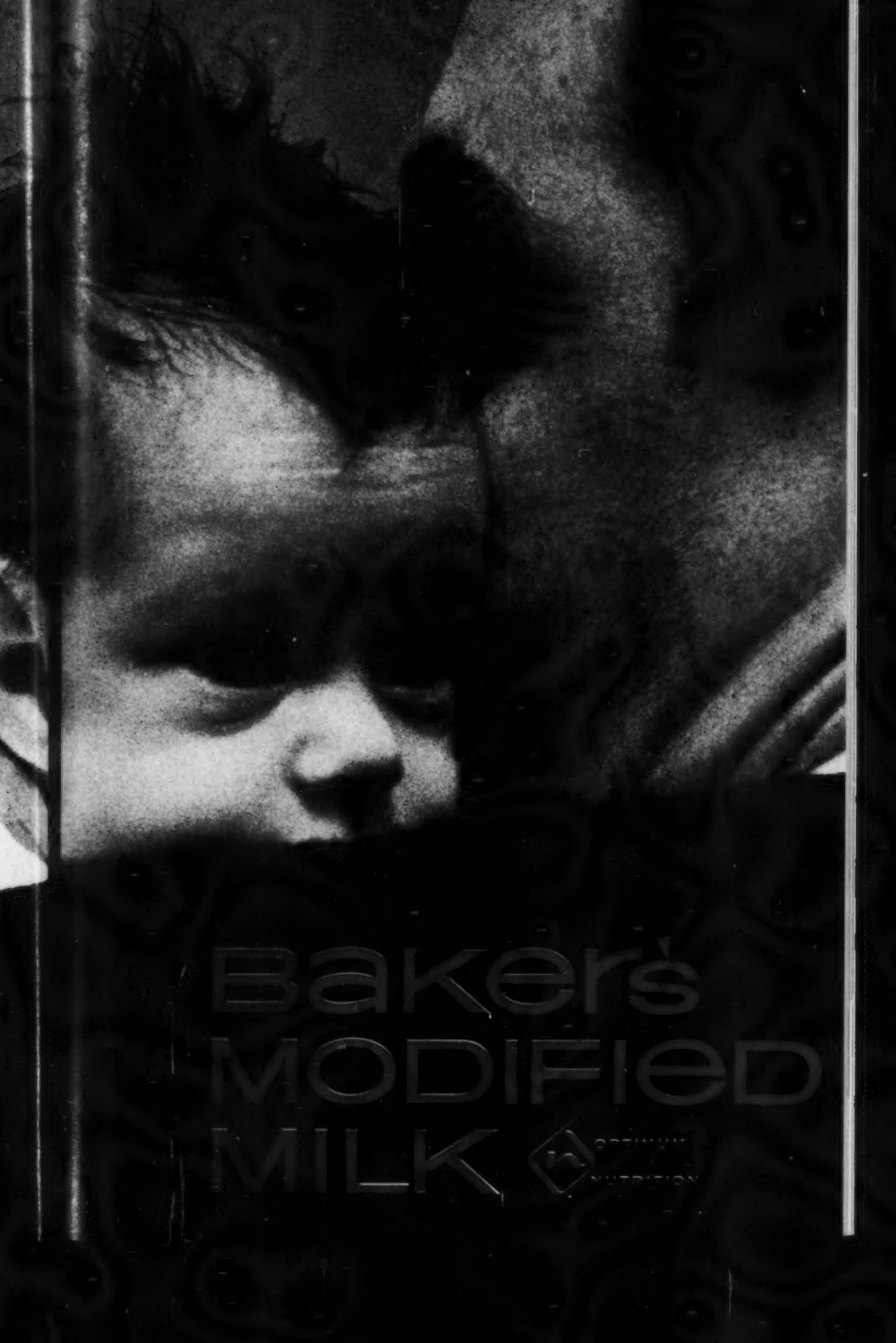
It has been shown that milk is an excellent vehicle for iron.

- absorption is high
- satisfactory hemoglobin responses are demonstrated
- digestive disturbances are minimized

Baker's Modified Milk supplies 7.5 mg. of iron per quart of formula at normal dilution —an important factor in Optimum Nutrition.*

*providing all the known dietary requirements plus a reserve.

THE BAKER LABORATORIES, INC.
Makers of VARAMEL — a flexible formula
CLEVELAND 3, OHIO


Baker's
MODIFIED
MILK
OPTIMUM
NUTRITION

Liquid antibiotic therapy

with just a suggestion of the flavor of cherry custard

Tetrex® Syrup

Tetracycline (Ammonium Polyphosphate Buffered) Syrup

Tetrex Syrup will be taken and liked by most arbitrary judges of flavored medications: small children and finicky adults.

Tetrex Syrup provides broad-spectrum antibiotic action against tetracycline-sensitive pathogens in a great variety of common infections. It is easily swallowed, readily absorbed, and the dosage can be accurately adjusted to meet individual requirements.

Tetrex Syrup is formulated in an *aqueous* vehicle, and has *no objectionable oily taste.* A further advantage: Tetrex Syrup *remains safely stable without refrigeration.*

Dosage: Children—Average daily dose about 12 mg. per pound of body weight, in divided doses at 6-hour intervals.
Adults—1 Gm., in divided doses of 2 teaspoonfuls (10 ml.) each at 6-hour intervals.

Supply: Tetrex Syrup—tetracycline (ammonium polyphosphate buffered) syrup equivalent to 125 mg. tetracycline HCl activity per 5-ml. teaspoonful. Bottles of 2 fl. oz. and 1 pint.

Other Tetrex dosage forms: Tetrex Pediatric Drops—tetracycline (ammonium polyphosphate buffered) syrup—equivalent to 100 mg. tetracycline HCl activity per ml. Bottles of 10 ml. with calibrated dropper to assure accurate dosage.

Tetrex-T/S—Tetracycline (ammonium polyphosphate buffered) syrup equivalent to 125 mg. tetracycline HCl activity per 5-ml. teaspoonful; plus 167 mg. each of sulfadiazine, sulfamerazine and sulfamethazine. Bottles of 2 fl. oz. (60 ml.)

Bristol
LABORATORIES INC.
SYRACUSE NEW YORK

WHY "WET THERAPY" FOR INFANTILE ECZEMA?

The first stages of infantile eczema (atopic dermatitis) are generally acutely inflamed and oozing. At this point the skin is most vulnerable to sensitization or to exacerbation by overtreatment. Authorities agree that *the blandest possible measures are indicated at this time and that soothing "wet" therapy is most appropriate.*

Senear and Haeberlin[1] consider Aveeno Colloidal Oatmeal baths to be a "basic wet therapy" in the acute stages of infantile eczema. Referring to the extreme pruritus, Crawford[2] states: "Colloidal baths . . . are most useful before bedtime. . . . A good commercial oatmeal preparation is Aveeno."

In a series of 41 infants and children with infantile eczema, Sompayrac and Ross[3] reported good improvement to complete clearing in 92% of the cases. They stated: "In many of the cases in which other medication produced meager or no results, there was rapid improvement when colloidal oatmeal baths were added without any change in prior medication."

A companion product to Aveeno Colloidal Oatmeal is Aveeno "Oilated." For chronic stages, Aveeno "Oilated" baths are specific. Aveeno "Oilated" contains, in addition to Aveeno Colloidal Oatmeal, 35% oils for extra emolliency. Dick[4] achieved "excellent" results with this product in 142 pediatric patients, 70 of whom presented dry, chronic stages of atopic dermatitis.

References:

1. Senear, F. E., and Haeberlin, J. B., Jr.: in M. Clin. North America, March 1958. Philadelphia, W. B. Saunders Company, pp. 489-496.
2. Crawford, L. V.: J. Pediatrics 53:99 (July) 1958.
3. Sompayrac, L. M., and Ross, C.: J. Florida M. A. 45:1411 (June) 1959.
4. Dick, L. A.: Arch. Pediat. 75:508 (Dec.) 1958.

TWO TYPES OF COLLOID BATHS FOR ALL STAGES OF THE ECZEMAS

. . . for acute, inflamed skin
AVEENO® Colloidal Oatmeal
Available in 16 oz. and 4 lb. boxes

/

. . . for dry, chronic stages
AVEENO® "OILATED"
Available in 10 oz. cans

AVEENO CORPORATION 250 West 57th Street New York 19, N. Y.

Pioneers in Ethically Promoted Colloid Baths

TAKE THE "EDGE" OFF

MACERATION

BUR-VEEN®

(Burow's with soothing Colloidal Oatmeal)

WET DRESSINGS

"GOVERNOR ACTION" reduces maceration, the major drawback in wet dressing therapy. The colloidal oatmeal in BUR-VEEN wet dressings lowers the osmotic pressure of the wet dressing and thus reduces the amount of water entering the skin cells.

BETTER TOLERATED than plain Burow's Solution. May be kept on longer and used more often without macerating the skin excessively.

SOOTHING TO INFLAMED SKIN by virtue of the colloidal oatmeal, which has well-documented anti-inflammatory and antipruritic effects.

BUR-VEEN Wet Dressing Powder is available in boxes of 6 and 100 packets. (One BUR-VEEN packet to one pint of water makes the equivalent of a 1:20 Burow's Solution with colloidal oatmeal.)

Active Ingredients: Aveeno® Colloidal Oatmeal, aluminum sulfate, calcium acetate.

LASSAR'S PASTE...*Modernized*

AVEENO OINTMENT

Aveeno Ointment, the modernized Lassar's Paste, is a soothing and protective colloidal oatmeal ointment for use in diaper rash, intertrigo and other common pediatric dermatoses.

Because it contains colloidal oatmeal in place of starch, Aveeno Ointment has distinct advantages over Lassar's Paste, namely, greater absorbent and adherent capacity with increased soothing quality.

AVEENO OINTMENT is available in 1 oz. and 4 oz. tubes.

ACTIVE INGREDIENTS: Aveeno Colloidal Oatmeal, zinc oxide and 0.5% hexachlorophene (to protect against bacterial invasion) . . . in an emollient base.

AVEENO CORPORATION **250 West 57th Street** **New York 19, N. Y.**

PROZINE offers the physician effective management of moderate to severe emotional disturbances encountered in children. Typical of the results obtainable with PROZINE were those recently reported by Ehrmantraut et al.[1] In a study of 176 disturbed children, the investigators conclude that PROZINE ". . . significantly reduced the incidence of abnormal behavior reactions. . . ."

By reducing motor excitability as well as anxiety and tension, the dual action of PROZINE helps the over-reactive child adjust to situations of stress. As a result, he becomes more responsive to guidance, more accessible to educational, psychiatric, or medical therapy.

1. Ehrmantraut, W., et al.: Scientific Exhibit Presented at the 11th Annual Meeting of the American Academy of General Practice, April 6-9, 1959, San Francisco, Calif.

once the most destructive boy in school

PROZINE*

meprobamate and promazine hydrochloride, Wyeth

SPECIFIC CONTROL THROUGH DUAL ACTION

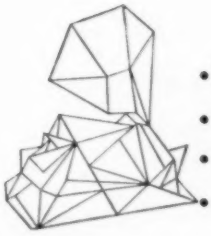
Wyeth

Philadelphia 1, Pa.

*Trademark

PURE ANTIHISTAMINE ACTION NOW A PHARMACOLOGIC FACT BECAUSE DĪSOMER SHEDS THE MOLECULAR DROSS

NEW...IN THE TREATMENT OF ALLERGIC DISORDERS



- *"...high therapeutic index"*[1]
- *unsurpassed clinical efficacy*
- *highly effective in exceptionally small doses*
- *side effects reduced to placebo level*

Disomer....a major scientific advance in the pharmacology of antihistamines!

DISOMER was described as being "*...as close to a pharmacologically pure form of histamine antagonist as the chemist can produce.*"[1] Incorporating the newest knowledge of structure-function relationships, DISOMER comes closest thus far to the therapeutic ideal of pure antihistamine activity. DISOMER represents the *d*-isomer of racemic brompheniramine maleate. In shedding the *l*-isomer a high point in clinical effectiveness is achieved while side effects are reduced to the placebo level.

Therapeutic results have been noteworthy with 94.7% effectiveness reported.[2] Equally noteworthy is the virtual absence of clinically significant adverse reactions. Indeed, the sole side effect reported was occasional, mild drowsiness in only 4.7% of patients.

With DISOMER your allergic patient remains your alert patient while enjoying unsurpassed freedom from allergic symptoms. Ready now for your prescription—DISOMER is available in a variety of dosage forms to fit your patients' individual requirements.

Availability:

DISOMER CHRONOTAB*	6 mg.
DISOMER CHRONOTAB*	4 mg.
DISOMER Tablets	2 mg.
DISOMER Syrup	2 mg. per 5 cc.

Usual dosage:

6 mg. CHRONOTAB	b.i.d.
4 mg. CHRONOTAB	t.i.d.
2 mg. Tablet	q.i.d.
Syrup 1 teaspoonful	q.i.d.

**Chronotab* is White's repeat-action tablet.

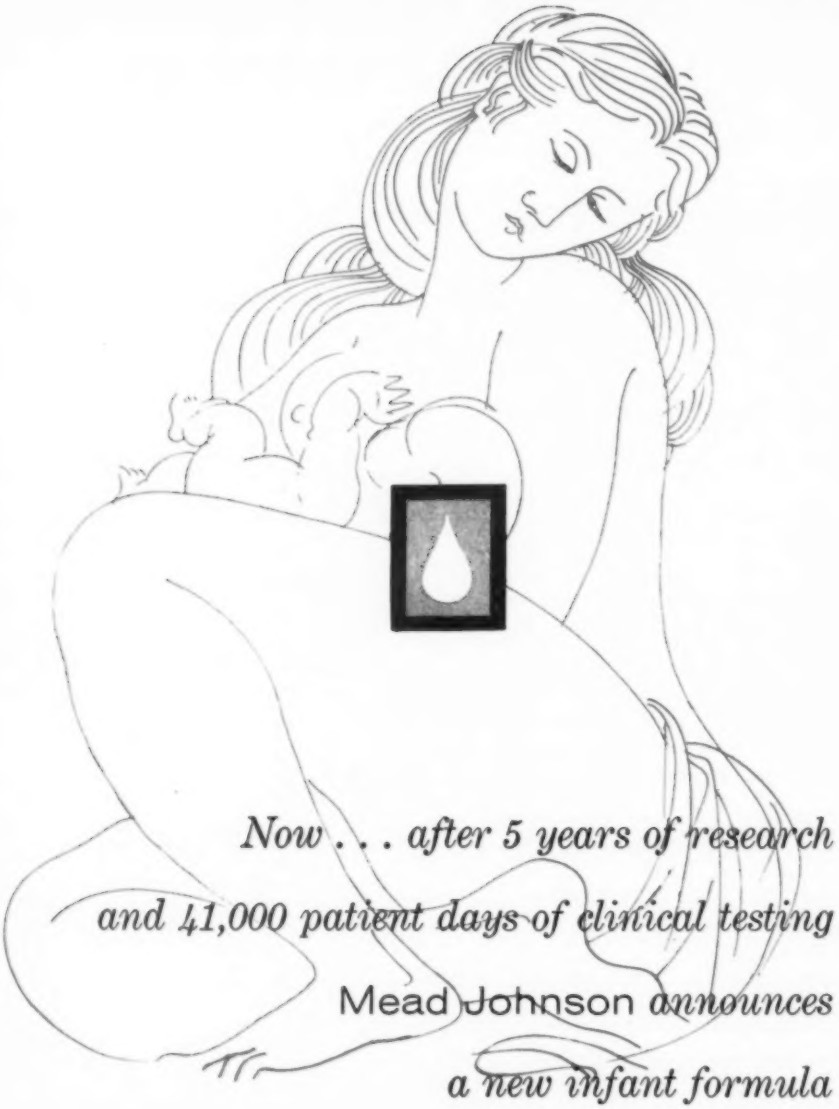
References: (1) Gould, A. H. and Long, D. L.: Clinical Pharmacology and Therapeutic Use of Dexbrompheniramine Maleate (Disomer), a new Histamine Antagonist (submitted for publication). (2) Medical Department, White Laboratories, Inc.

WHITE LABORATORIES, INC.
Kenilworth, New Jersey

DISOMER

DEXBROMPHENIRAMINE MALEATE

...sheds the molecular dross



Now . . . after 5 years of research

and 41,000 patient days of clinical testing

Mead Johnson *announces*

a new infant formula

nearest to mother's milk[1]

in nutritional breadth and balance

Enfamil*

Infant formula

nearest to mother's milk[1]

in nutritional breadth and balance

In a well controlled institutional study[2], using the Latin Square technic† for the first time in infant nutritional research, Enfamil was compared with three widely used infant formula products.

This formula produced:

weight gains greater than the over-all average for the study.
stool firmness between firm and soft . . . and lower stool frequency.

There is no product nearer to mother's milk in nutritional breadth and balance:

. . . in its pattern of protein, fat and carbohydrate by caloric distribution

. . . in its pattern of vitamins and minerals (more vitamin D in accordance with NRC recommendations)

. . . in its fat composition (no butterfat; no sour regurgitation)

. . . in its ratio of saturated to unsaturated fatty acids

. . . in its low renal solute load

ENFAMIL LIQUID—cans of 13 fluid ounces.
1 part Enfamil Liquid to 1 part water for 20 cal. per fl. oz.

ENFAMIL POWDER—cans of 1 lb., with measure.
1 packed level measure of Enfamil Powder to 2 ounces of water for 20 cal. per fl. oz.

†The Latin Square technic, used for the first time in infant nutritional research to evaluate Enfamil, is a change-over method for intensive, controlled clinical testing which was applied to infants during their critical first 8 weeks of life. It is an efficient way of neutralizing the multiple variables in nutritional research.

1. Macy, I. G.; Kelly, H. J., and Sloan, R. E., with the Consultation of the Committee on Maternal and Child Feeding of the Food and Nutrition Board, National Research Council: The Composition of Milks. National Academy of Sciences, National Research Council, Publication 254, Revised 1953. 2. Research Laboratories, Mead Johnson & Company.

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- **Streptococcal and Pneumococcal Infections**[1-8]
- **Rheumatic Fever Prophylaxis**[9-18]
- **Syphilis (primary & secondary) and Gonorrhea**[19-25]

Representative References: 1. Breese, B.B.: J.A.M.A. **152**:9 (May 2) 1953. 2. Breese, B.B., and Disney, F.A.: Pediatrics **15**:516 (May) 1955. 3. Davis, J., and Schmidt, W.C.: New England J. Med. **256**:339 (Feb. 21) 1957. 4. Feldman, H.A., et al.: J.A.M.A. **155**:109 (May 8) 1954. 5. Githens, J.H., et al.: Antibiot. Med. & Clin. Therap. **4**:333 (June) 1957. 6. McFarland, R.B., et al.: New England J. Med. **258**:1277 (June 26) 1958. 7. Mohler, D.N., et al.: New England J. Med. **254**:45 (Jan. 12) 1956. 8. Morris, A.J., and Rammelkamp, C.H., Jr.: J.A.M.A. **165**:664 (Oct. 12) 1957. 9. American Heart Association: Circulation **15**:154 (Jan.) 1957. 10. Diehl, A.M., et al.: South. Med. J. **49**:250 (March) 1956. 11. Diehl, A.M., et al.: J.A.M.A. **155**:1466 (Aug. 21) 1954. 12. Giddings, L.E., and Yoder, F. D.: Rocky Mt. Med. J. **56**:37 (Jan.) 1959. 13. Houser, H. B.: J. Mich. Med. Soc. **52**:1289 (Dec.) 1953. 14. Mortimer, E.A., Jr., et al.: New England J. Med. **260**:101 (Jan. 15) 1959. 15. Stollerman, G.H.: Am. Pract. & Digest Treat. **5**:589 (Aug.) 1954. 16. Stollerman, G.H., et al.: Antibiotics Annual 1953-1954, Medical Encyclopedia, Inc., pp. 114-118. 17. Stollerman, G.H., and Rusoff, J.H.: J.A.M.A. **150**:1571 (Dec. 20) 1952. 18. Wood, H.F., et al.: Am. Heart Assoc., 29th Scientific Sessions, Oct. 26-29, 1956. 19. Landman, G.S., et al.: South. Med. J. **51**:891 (July) 1958. 20. Montgomery, C.H., et al.: Texas State J. Med. **54**:575 (Aug.) 1958. 21. Moore, J. E.: Ann. Int. Med. **39**:644 (Sept.) 1953. 22. O'Brien, J.F., and Smith, C.A.: Am. J. Syph., Gonorr. & Ven. Dis. **36**:519 (Nov.) 1952. 23. Smith, C.A., et al.: Am. J. Syph., Gonorr. & Ven. Dis. **38**:136 (March) 1954. 24. Takos, M.J., et al.: Public Health Reports **72**:976 (Nov.) 1957. 25. Thomas, E.W.: J.A.M.A. **162**:1536 (Dec. 22) 1956.

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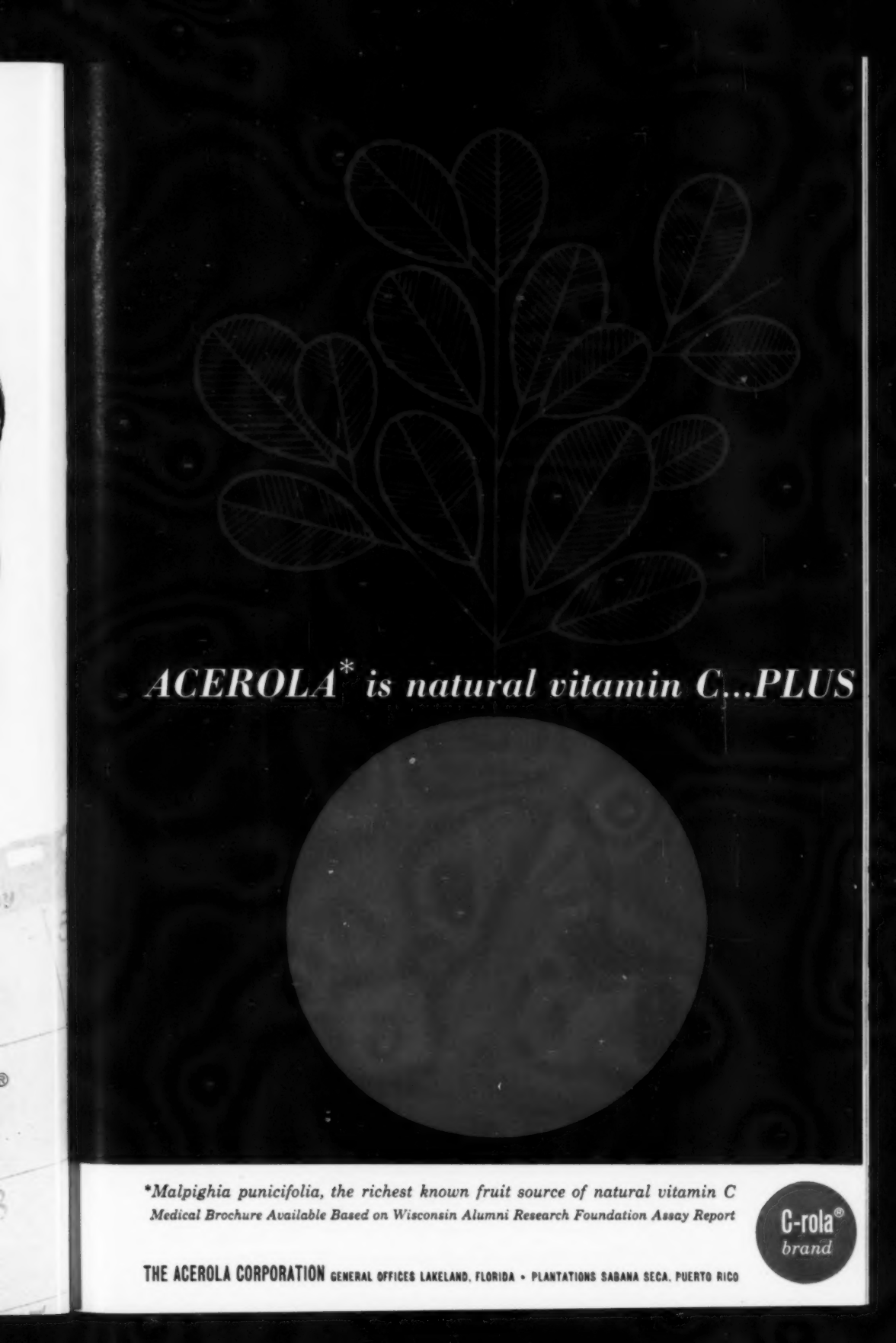
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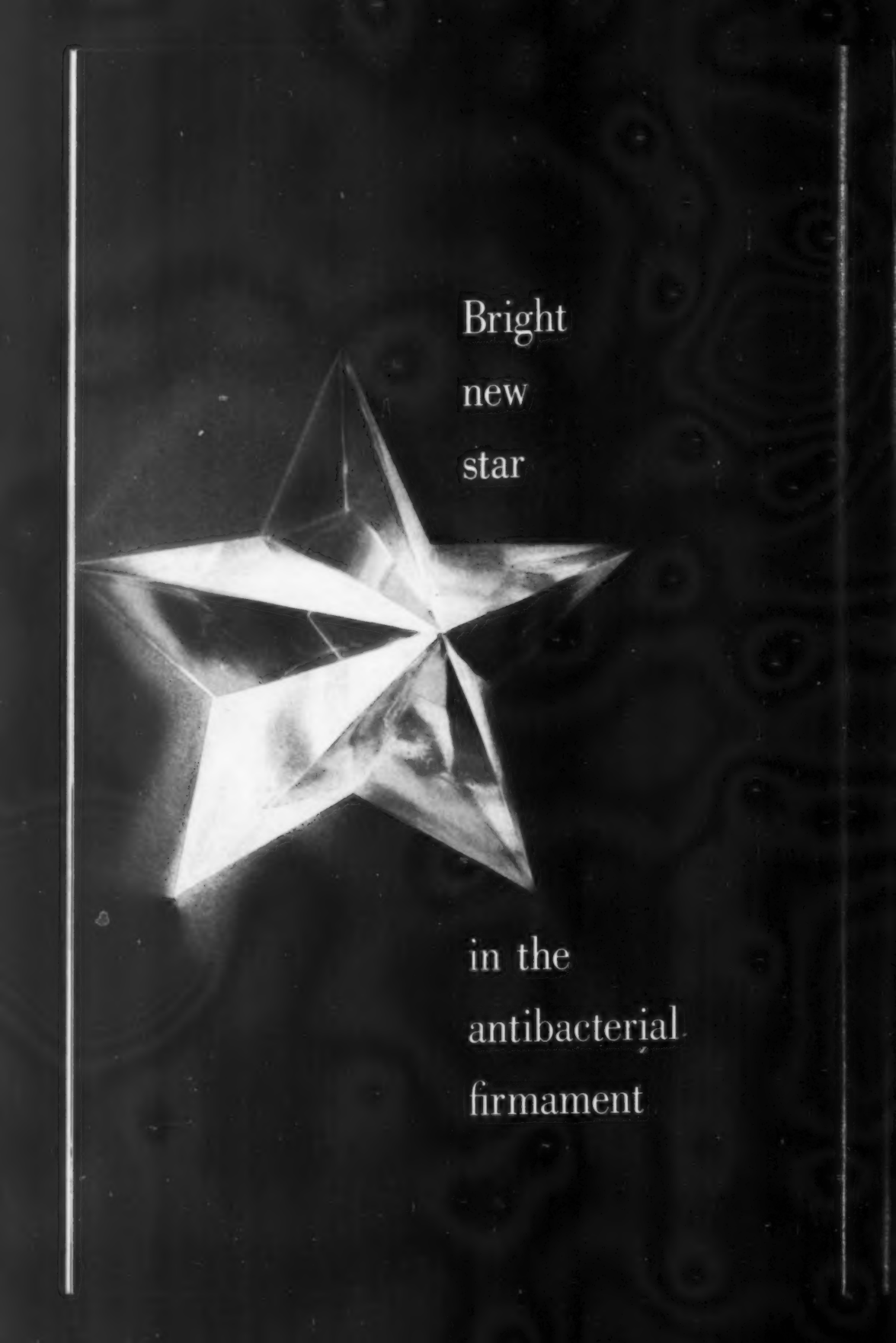
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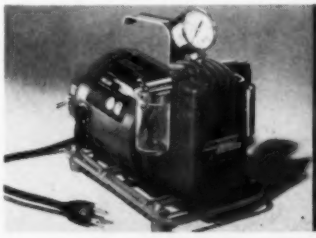
1. Kirkwood, E. S.: Nursing World 129:8, 1955.



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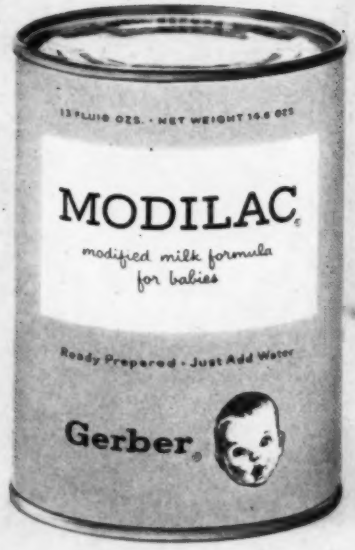

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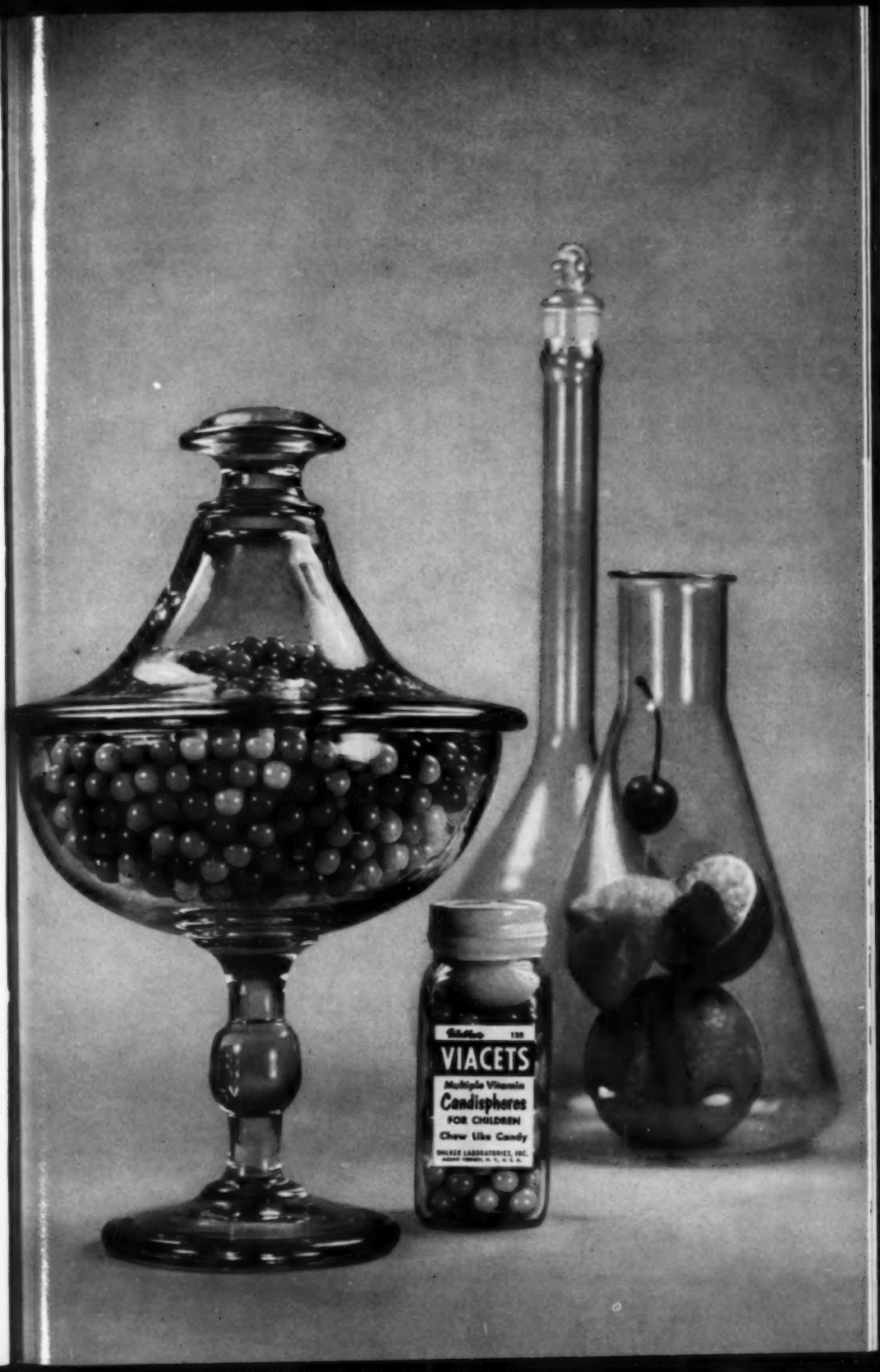
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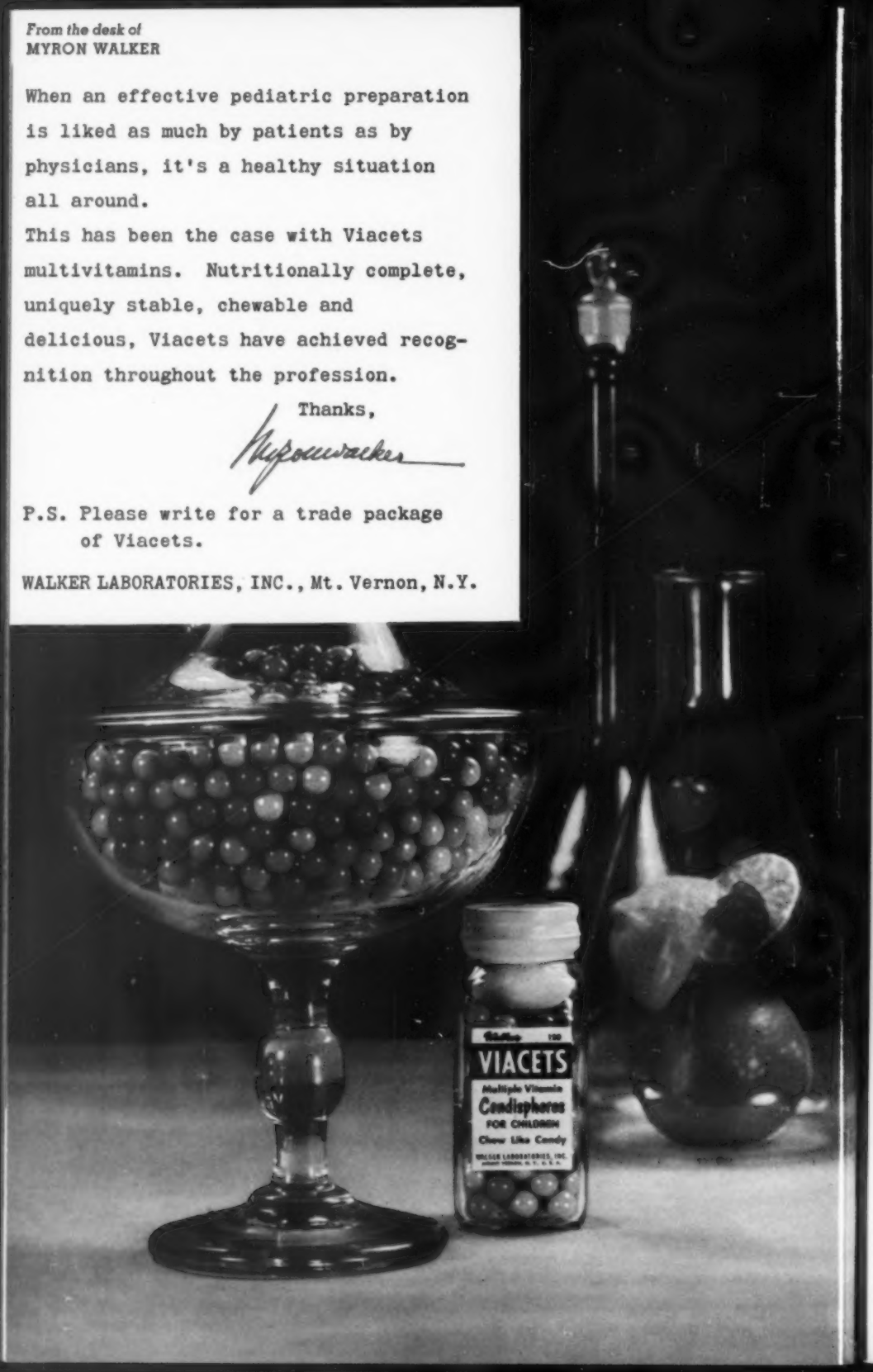

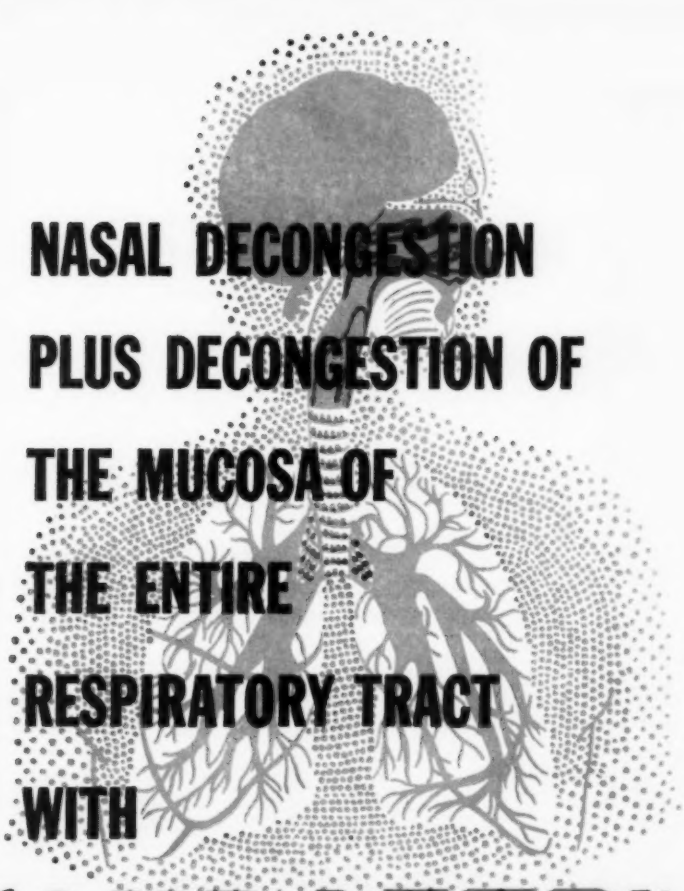

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Lattimer, John K., and Spirito, A. L.: Clorpactin for Tuberculosis cystitis: Instrument sterilization, *Journ. of Urology*, Vol. 73, No. 6, June, 1955. • Wolinsky, E., Smith, M. M. and Steenkun, Wm. Jr., Tuberculocidal Activity of Clorpactin. A New Chlorine Compound, *Antibiotic Medicine*, 1:382-384, July, 1955. • Sanders, Murray and Soret, M. G.: Virucidal activity of WCS-90, *Antibiotics and Chemotherapy*, Vol. V, No. 11, Nov. 1955. • Gliedman, M. L., Lt. (MC) USNR, Grant, R. N. Capt. (MC) USN, Vestal, B.L., B.S., and Karlson, K. E., M.D.; Impromptu Bowel Cleansing and Sterilization, *Surgery*, 43:282-287. • From The Textbook, Extracorporeal Circulation, Edited by Dr. J. Garrott Allen, Page 87; Charles C. Thomas, Publisher.

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1. Phelps, W. M.: Arch. Pediat. 76:249 (June) 1959. 2. Spears, C. E., and Phelps, W. M.: Arch. Pediat. 76:287 (July) 1959

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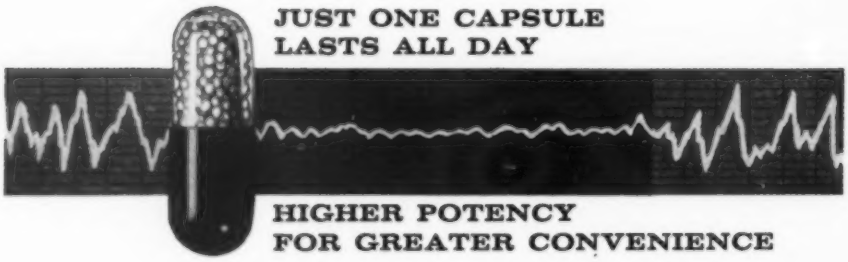

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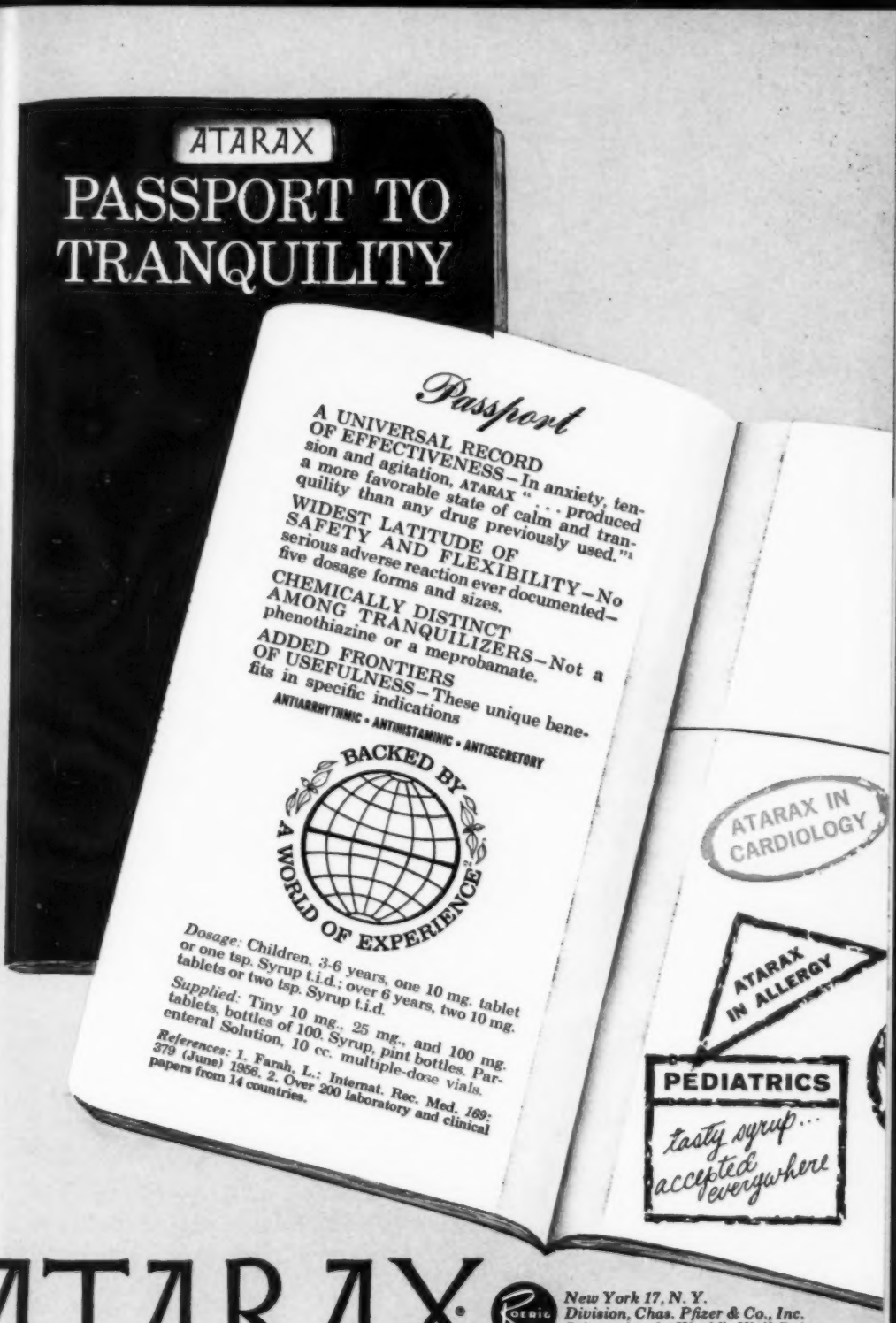
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References: 1. Farah, L.: Internat. Rec. Med. 169: 379 (June) 1956. 2. Over 200 laboratory and clinical papers from 14 countries.
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1. Cooke, R. E.: J. Pediat. **54**:548 *(April) 1959.*

2. Hill, L. F.: J. Pediat. **54**:545 *(April) 1959.*

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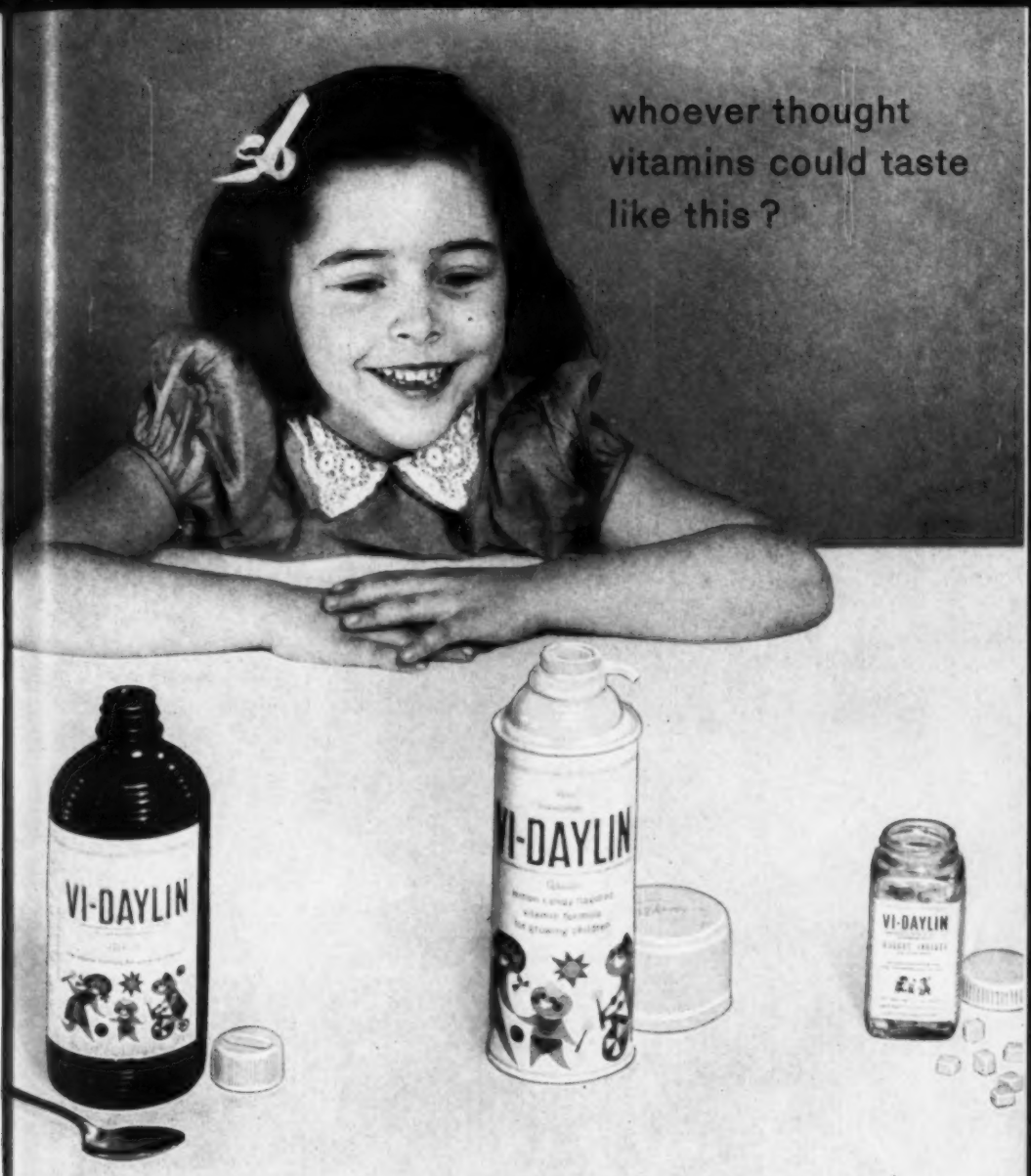

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All the essential vitamins . . . in delicious, lemon-candy flavored form

VI-DAYLIN—Vitamins A, D, B_1, B_2, B_6, B_{12}, C and Nicotinamide, Abbott. DULCET—Sweetened Tablets, Abbott

912179

Resolves children's cough

ROMILAR CF treats the entire cough complex—**Romilar (dextromethorphan)** raises the cough-reflex threshold promptly (15-30 minutes) for as long as six hours; provides safe, efficient, specific cough relief without respiratory depression, without constipation, without any other narcotic complication[1-9] — **phenylephrine** lessens bronchial and nasal congestion — **chlorpheniramine** relieves allergic symptoms — **N-acetyl-p-aminophenol** reduces pain and fever.

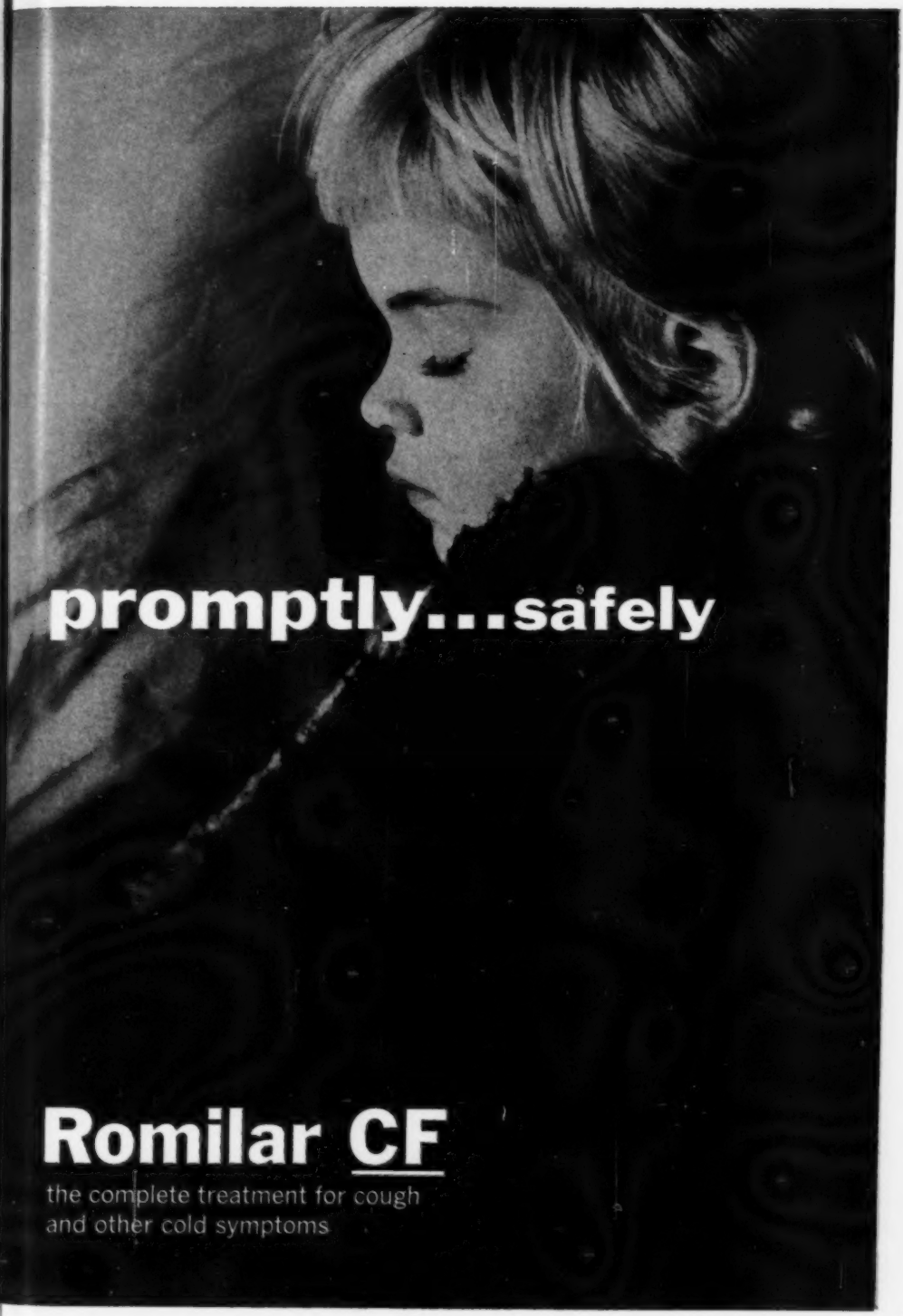
SUPPLY: Romilar CF Syrup in bottles of 16 oz and 1 gal.
Romilar CF Capsules in bottles of 100.

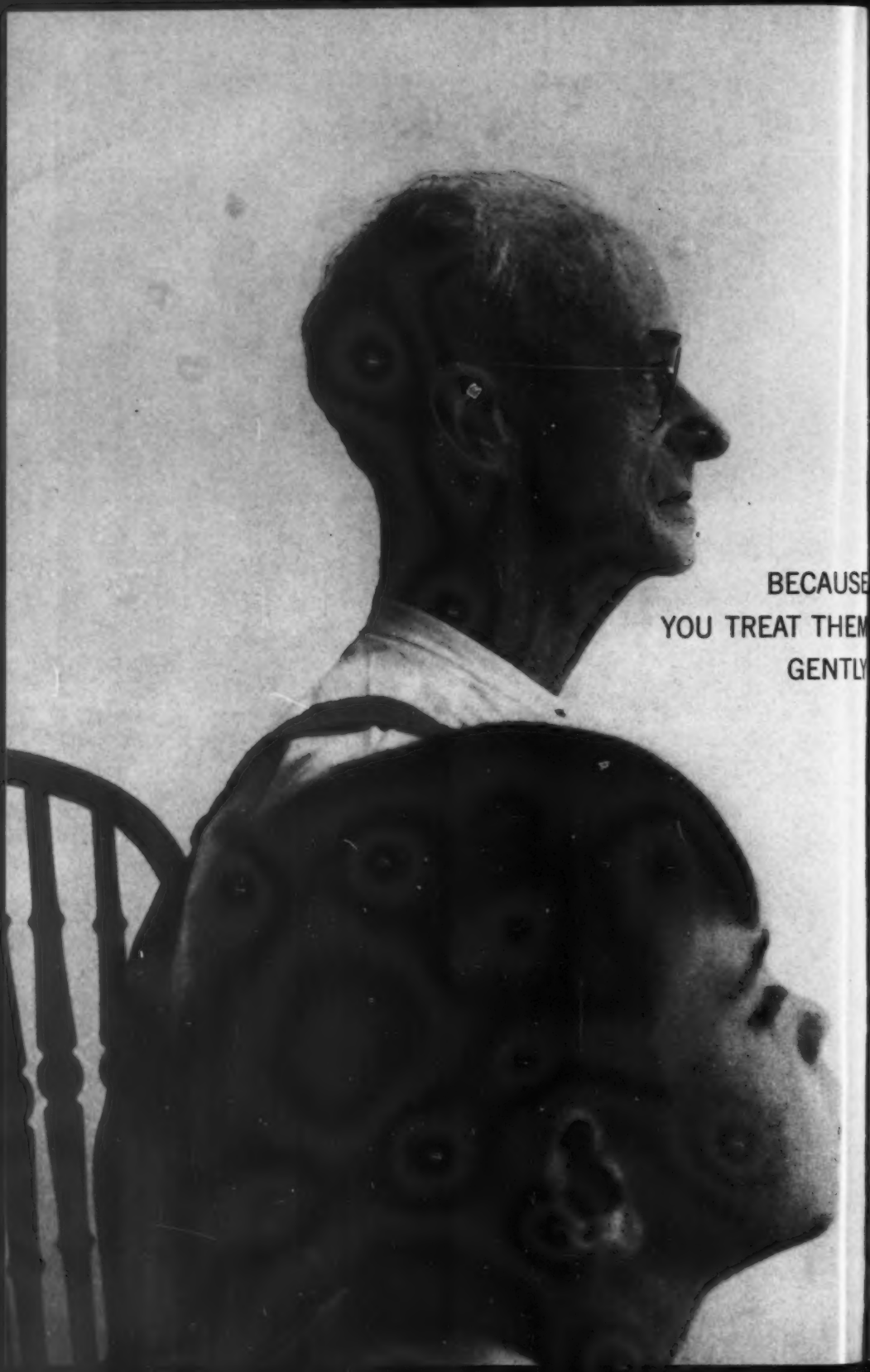
Bibliography: (1) N. Ralph, Am. J. M. Sc. 227:297, 1954. (2) H. A. Bickerman, In W. Model, Ed., Drugs of Choice 1958-1959, St. Louis, The C. V. Mosby Company, p. 556. (3) H. A. Bickerman, E. German, B. M. Cohen and S. Itkin, Am. J. M. Sc. 234:191, 1957. (4) L. J. Cass, W. S. Frederik and J. B. Andosca, Am. J. M. Sc. 227:291, 1954. (5) L. J. Cass and W. S. Frederik, J. Lab. & Clin. Med. 48:879, 1956. (6) L. J. Cass and W. S. Frederik, New England J. Med. 249:132, 1953. (7) H. Isbell and H.F.Fraser, J. Pharmacol. & Exper. Therap. 107:524, 1953. (8) W. M. Benson, P. L. Stefko and L. O. Randall, J. Pharmacol. & Exper. Therap. 109:189, 1953. (9) New and Nonofficial Drugs 1959, Philadelphia, J. B. Lippincott Company, p. 326.

When only the antitussive action of dextromethorphan is indicated, ROMILAR (syrup, tablets or expectorant) provides specific, dependable relief.

Romilar® Hydrobromide — brand of dextromethorphan hydrobromide.

ROCHE LABORATORIES • Division of Hoffmann-La Roche Inc • Nutley 10, N.J.


promptly...safely
Romilar CF
the complete treatment for cough
and other cold symptoms


BECAUSE
YOU TREAT THEM
GENTLY

"In no case . . .
was there any rebound congestion."[1]

Your youngest patient as well as your oldest will find new Otrivin an unusually gentle yet remarkably effective nasal decongestant. Otrivin works quickly; its action is prolonged. Typical of many clinicians' reports is the one published by Kolodny[1]: Of 64 patients studied, 92 per cent had good or excellent results. "In no case studied was there any rebound congestion. Local side effects were minimal. . . . Extremely few systemic effects occurred. . . ."

NEW
OTRIVIN® FOR GENTLE RELIEF OF STUFFY NOSE
ON PRESCRIPTION ONLY

Otrivin is safe even for the very young. "The particularly striking feature of Otrivin solution was the absence of side effects, even in infants as young as two weeks."[2] "It is effective in low concentrations and is a safe nasal vasoconstrictor for even the young patient."[3]

SUPPLIED: Otrivin *Nasal Solution*, 0.1%; dropper bottles of 1 ounce. Otrivin *Nasal Spray*, 0.1%; plastic squeeze tubes of 15 ml. Otrivin *Pediatric Nasal Spray*, 0.05%; plastic squeeze tubes of 15 ml.

REFERENCES: 1. Kolodny, A. L.: Antibiotic Med. *6*:452 (Aug.) 1959. 2. Davis, M. R.: To be published. 3. Pelusc, S.: In press.

Otrivin® hydrochloride (xylometazoline hydrochloride CIBA) 2/2753MK

CIBA SUMMIT, N. J.

FOR NATURAL TRANQUILITY FEED BREMIL®

NEW LIQUID AND POWDERED

Guaranteed physiologic Ca:P ratio of 1½:1 (not available in any other liquid infant formula product). Comparable to breast milk, more physiologic than cow's milk—minimizes restlessness, wakefulness, excessive crying.

Easy for mothers—just add water

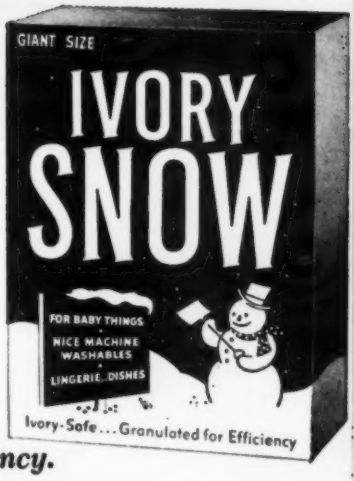
PHARMACEUTICAL DIVISION 350 Madison Avenue, New York 17

BREMIL • MULL-SOY • DRYCO • BETA LACTOSE • KLIM

AND FOR THOSE WHO CAN'T "TAKE" MILK... *MULL-SOY*®

Why should you recommend Ivory Snow for baby's wash?

1. **Because it's as safe a soap as a mother can use . . .** leaves diapers and baby clothes soft, gentle-clean . . . and completely free from irritating deposits that can chafe tender skin!
2. **Because it's as practical for mother as it is safe for baby—** the only soap that gives a busy mother Ivory-safety in the efficient granulated form she needs for today's washing machines!

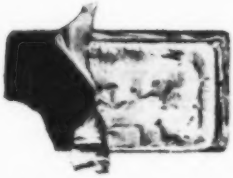


Only Ivory Snow is Ivory-safe and granulated for machine efficiency.

99 44/100% PURE® with Beauty Glow. A PROCTER & GAMBLE PRODUCT

no more battles at vitamin time

Delectavites®



delectable, chewable, chocolate-like vitamin-mineral nuggets

No fights, no battles at vitamin time because children love to chew DELECTAVITES. These delectable, easily chewable chocolate nuggets supply all essential vitamins as well as minerals so necessary during the years of growth. As soon as children can chew, they can go directly from vitamin drops to DELECTAVITES. And, *now* you can be sure your little patients will follow your instructions about taking their daily vitamins.

Each nugget contains: Vitamin A—5000 Units* / Vitamin D—1000 Units*/ Vitamin C—75 mg. / Vitamin E—2 Units† Vitamin B_1—2.5 mg. / Vitamin B_2—2.5 mg. / Vitamin B_6—1 mg. / Vitamin B_{12} Activity—3 mcg. / Panthenol—5 mg. Nicotinamide—20 mg. / Folic Acid—0.1 mg. / Biotin—30 mcg. / Rutin—12 mg. / Calcium Carbonate—125 mg. / Boron—0.1 mg. / Cobalt—0.1 mg. / Fluorine—0.1 mg. / Iodine—0.2 mg. / Magnesium—3.0 mg. / Manganese—1.0 mg. / Molybdenum —1.0 mg. / Potassium—2.5 mg. *U.S.P. UNITS †INT. UNITS

dosage: one Delectavites daily. **supply:** Box of 30 (one month's supply), Box of 90 (three months' supply).

WHITE LABORATORIES, INC., KENILWORTH, NEW JERSEY

there hardly seems an excuse for having a runny nose these days

The youngster who stops sniffling and begins breathing freely in a few minutes with all air passages cleared...and no sense of jitteriness or nasal irritation...is experiencing the Novahistine Effect.

Each 5 cc. teaspoonful of good-tasting Novahistine Elixir contains: phenylephrine HCl, 5.0 mg. and prophenpyridamine maleate, 12.5 mg. And the distinctly additive action achieved by combining this orally effective vasoconstrictor and superior antihistamine usually controls cold symptoms better than any single drug.

Novahistine® Elixir

PITMAN-MOORE COMPANY Division of Allied Laboratories, Inc., Indianapolis 6, Indiana

safety
efficacy
economy
rapidity
dependability
adaptability

Gantrisin... the quality of greatness

Reports in hundreds
of leading journals and
scores of standard textbooks
reflect the position of Gantrisin as drug
of choice in urinary and other bacterial infections.

ROCHE LABORATORIES

Division of Hoffmann-La Roche Inc • Nutley 10 • N. J.

GANTRISIN®—brand of sulfisoxazole ROCHE®

first in preference for cough relief

quiets the cough

calms the patient

expectorant antihistaminic sedative topical anesthetic

PHENERGAN® EXPECTORANT

Promethazine Expectorant, Wyeth with codeine plain (without codeine)

NON-NARCOTIC PEDIATRIC FORMULA: Pediatric

PHENERGAN Expectorant with Dextromethorphan, Wyeth

Wyeth®

Philadelphia 1, P

THE SAFEST ORAL IRON

... because of chelation

FERROLIP® PEDIATRIC DROPS

(Iron Choline Citrate Chelate)

An official A.M.A. report[1] has stressed the toxicity of ferrous sulfate and other dissociable iron salts, particularly on accidental overdosage. By presenting iron as a *chelate*, FERROLIP minimizes the danger of excessive systemic absorption, as compared with ferrous sulfate and gluconate.[2]

In addition, because of chelation, FERROLIP is well tolerated even on an empty stomach, mixes freely in milk, formula, or juice, will not stain or damage teeth. Clinically confirmed as an effective hematinic.[2]

DOSAGE: Infants and younger children, 9 drops (0.5 cc.) daily. Older children and adults, 18 drops (1 cc.) daily. Each cc. contains 0.208 gram iron choline citrate chelate,* equivalent to 25 mg. of elemental iron.

SUPPLIED: 30-cc. unbreakable plastic squeeze bottles.

ALSO AVAILABLE: **FERROLIP** Tablets; **FERROLIP** Syrup; **FERROLIP ob** Tablets; **FERROLIP plus** Capsules and Liquid.

1. A.M.A. Committee on Toxicology: J.A.M.A. 6:676, 1959. 2. Franklin, M., et al.: Chelate Iron Therapy, J.A.M.A. 166:1685, 1958.

*U.S. Pat. 2,575,611

Flint, EATON & COMPANY
Decatur, Illinois

new dropper tip

Gentle pressure releases precise dosage drop by drop.

new potency

Each cc. now provides equivalent of 25 mg. elemental iron.

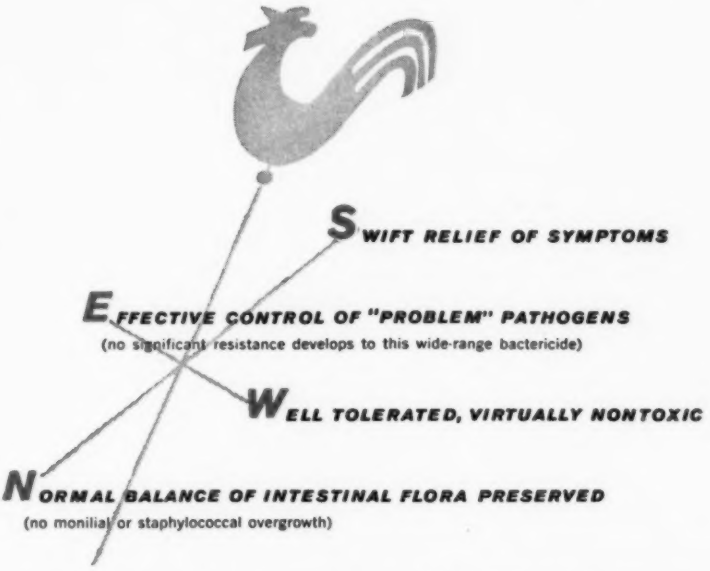
TO STOP DIARRHEA

from all points... growing evidence favors

FUROXONE®

brand of furazolidone

▪ Pleasant-flavored LIQUID, 50 mg. per 15 cc. (with kaolin and pectin) ▪ Convenient TABLETS, 100 mg. ▪ Dosage—400 mg. daily for adults, 5 mg./Kg. daily for children (in 4 divided doses).


SWIFT RELIEF OF SYMPTOMS
EFFECTIVE CONTROL OF "PROBLEM" PATHOGENS
(no significant resistance develops to this wide-range bactericide)
WELL TOLERATED, VIRTUALLY NONTOXIC
NORMAL BALANCE OF INTESTINAL FLORA PRESERVED
(no monilial or staphylococcal overgrowth)

From a Large Midwestern University: FUROXONE Controls Antibiotic-Resistant Outbreak. An outbreak of bacillary dysentery due to Shigella sonnei was successfully controlled with FUROXONE after a broad-spectrum antibiotic had proved inadequate. Cure rates (verified by stool culture) were 87% with FUROXONE, 36% with chloramphenicol. Only FUROXONE "failures" were those lost to follow-up. Chloramphenicol failures subsequently treated with FUROXONE responded without exception. FUROXONE was also used effectively as prophylaxis and to eliminate the carrier state. It was "extremely well tolerated in all 191 individuals who received it either prophylactically or therapeutically."

Galeota, W. R., and Moranville., B. A.: Student Medicine (in press)

THE NITROFURANS—A UNIQUE CLASS OF ANTIMICROBIALS EATON LABORATORIES, NORWICH, NEW YORK

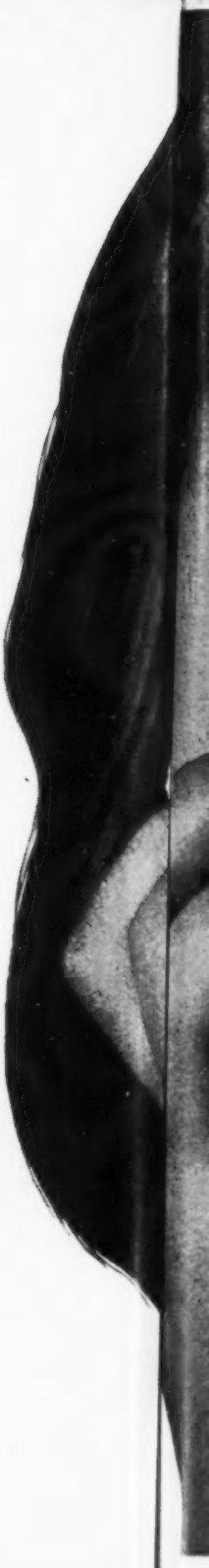
bed time,
story time,
Syrup Phenergan Fortis time
for a sick child.

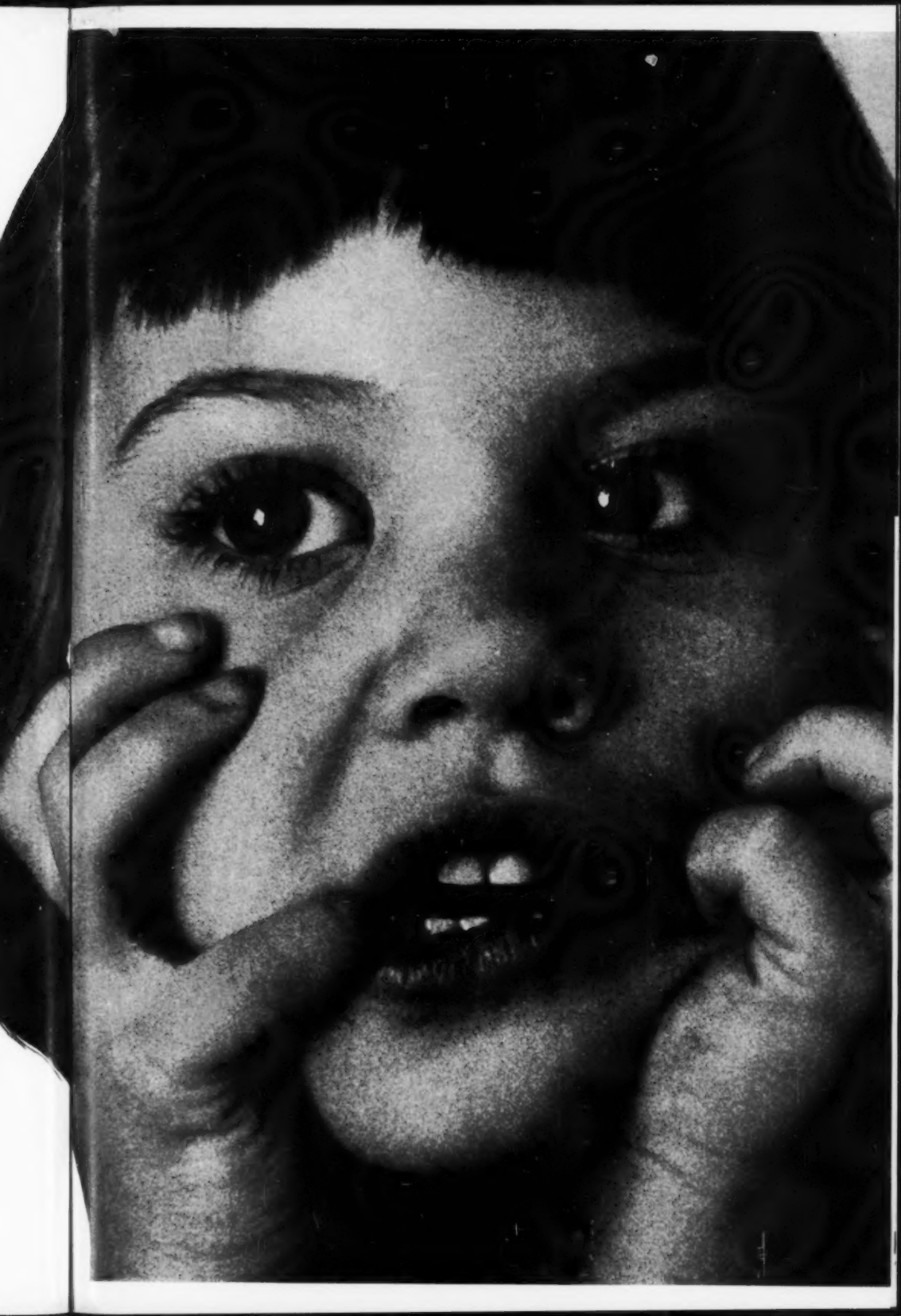
Syrup Phenergan Fortis
calms the restless child,
controls nausea and vomiting,
eases itching,
quiets coughing.

children
like the cream-mint flavor
of Syrup Phenergan Fortis,
parents
like the way it's accepted,
physicians
like the comfort it provides—
and the minimal side-effects.

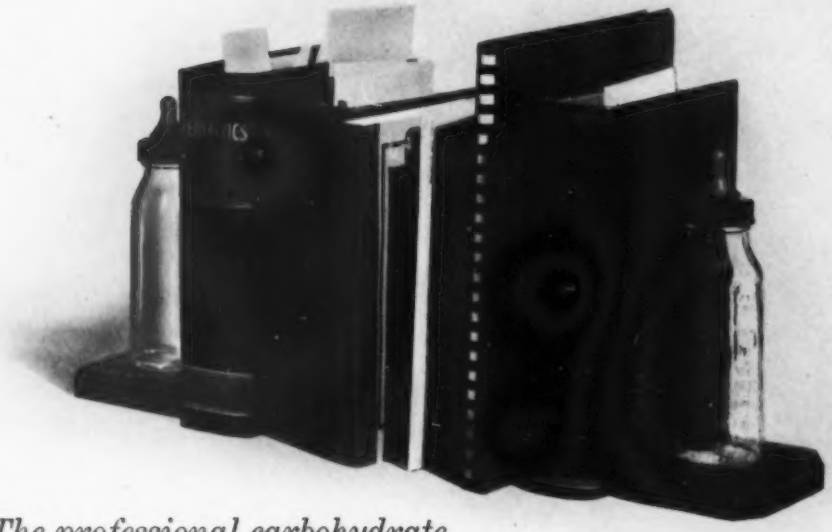
SYRUP
PHENERGAN® FORTIS
HYDROCHLORIDE
Promethazine Hydrochloride, Wyeth

Wyeth®
Philadelphia 1, Pa.





BACKGROUND FOR CONFIDENCE



The professional carbohydrate for milk modification

Dextri-Maltose®

Carbohydrate formula modifier, Mead Johnson

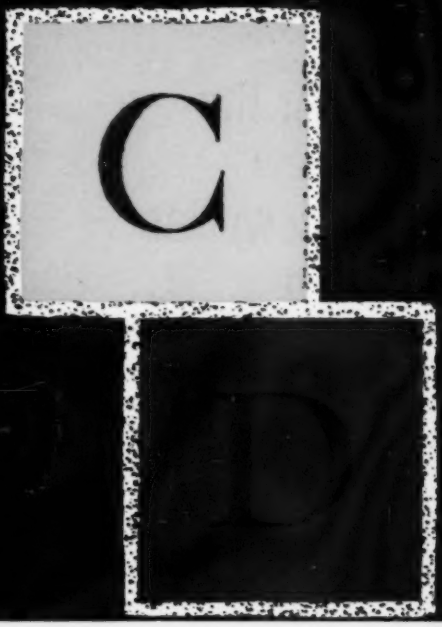
Cow's milk, water and carbohydrate—the one system of infant feeding that consistently, for over four decades—has received universal pediatric recognition. No carbohydrate employed in this system of infant feeding enjoys so rich and enduring a background of clinical acceptance as Dextri-Maltose.

Dextri-Maltose is

- *non-sweet* . . . won't develop "sweet tooth"
- *economical* . . . costs only pennies a day
- *easy-to-use* . . . dry powder form is easy to measure accurately; dissolves readily

Mead Johnson
Symbol of service in medicine

a new viewpoint on pediatric vitamin supplements



"J.A.M.A." 169:41-5
(January 3, 1959)

An Abstract of

COUNCIL ON FOODS AND NUTRITION
"Vitamin Preparations As Dietary Supplements and As Therapeutic Agents"

The A.M.A. Council on Foods and Nutrition recommends an intake of 30 mg. vitamin C and 400 USP units vitamin D in the daily diets of normal healthy infants.

The supplementation of vitamin D should not exceed 400 USP units daily throughout the growth period; as larger amounts decrease appetite and, as a consequence, reduce the total retention of calcium and phosphorus and slow linear growth.

An adequate supplementation of vitamin C should be started with the introduction of artificial or breast feeding.

The Council also states that present supplementations of vitamin D are too large..... and vitamin A and the B complex not necessary for routine use.

"PEDIATRICS" 23:833
(May, 1959)

An Abstract of

EDITORIAL—Charles D. May
"Vitamin Supplements"

A recent editorial in "PEDIATRICS" quotes the most pertinent part of the A.M.A. Council on Foods and Nutrition Report in full; underscores the fact that a normal infant requires no more than 30 mg. vitamin C and 400 USP units vitamin D in the supplementation of mother's milk or artificial formula; and points out that a supplement is a supplement and not the whole source of supply.

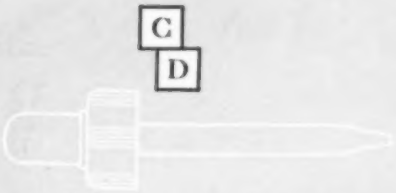
A growing child should be introduced to a wide variety of wholesome food, since food is the normal source of nutrients.

The editorial warns against the temptation to give every infant and child a superabundance of vitamins in an all inclusive supplement—just to be sure. And ends up by encouraging economy in the use of vitamin supplements in order to provide more food and education.

NEW PRODUCT ANNOUNCEMENT

now

for the new viewpoint on pediatric vitamin supplements



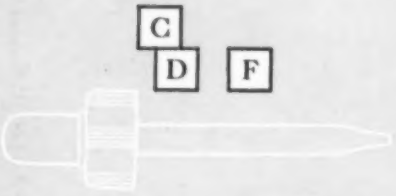
ECONOMICAL
affords at least
30% savings.

fundamental vitamin supplement

Funda-Vite™

PEDIATRIC DROPS

Each 0.6 ml. contains 400 USP units vitamin D and 30 mg. vitamin C to supplement the diets of normal healthy infants and children. This formulation is based on the new viewpoint on pediatric vitamin supplements[1,2]. *Available in 30 ml. bottles with calibrated dropper.*



Fluorine added
at no additional cost.

fundamental vitamin supplement plus fluorine

Funda-Vite (F)™

PEDIATRIC DROPS

Each 0.6 ml. contains 400 USP units vitamin D, 30 mg. vitamin C and 0.5 mg. fluorine (as sodium fluoride) to supplement the diets of normal healthy infants and children... safeguarding against nutritional deficiencies and future dental caries[3]. FOR USE IN COMMUNITIES WITHOUT FLUORIDATION OF DRINKING WATER. *Available in 30 ml. bottles with calibrated dropper.*

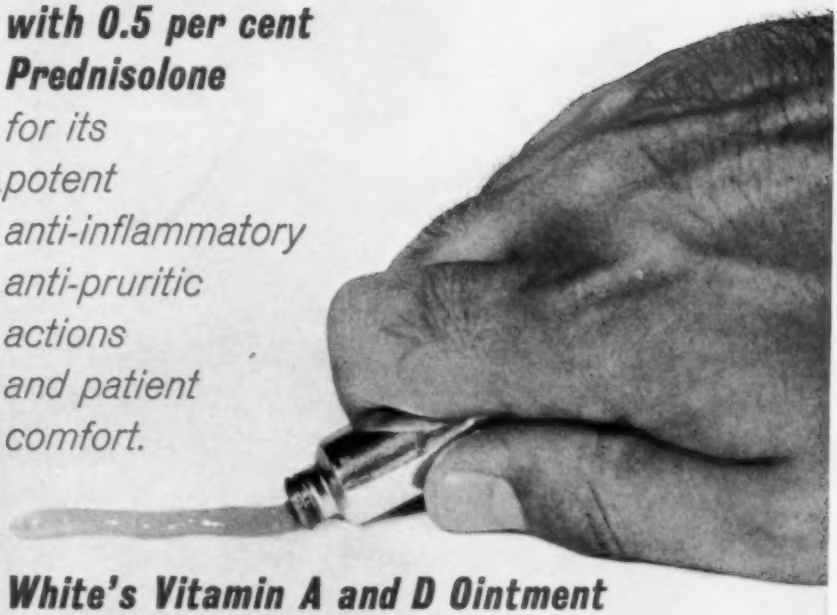
REFERENCES: 1. Council On Foods and Nutrition: Vitamin Preparations As Dietary Supplements and As Therapeutic Agents J.A.M.A. 169:41-8 (Jan. 3) 1959. 2. Editorial: Vitamin Supplements, May, C.D., Pediatrics 23:833 (May) 1959. 3. Council On Dental Therapeutics: Prescribing Supplements of Dietary Fluorides, J. Am. Dental Assoc. 56:589-591 (April) 1958.

HOYT

SAMPLES AND LITERATURE—write Medical Department

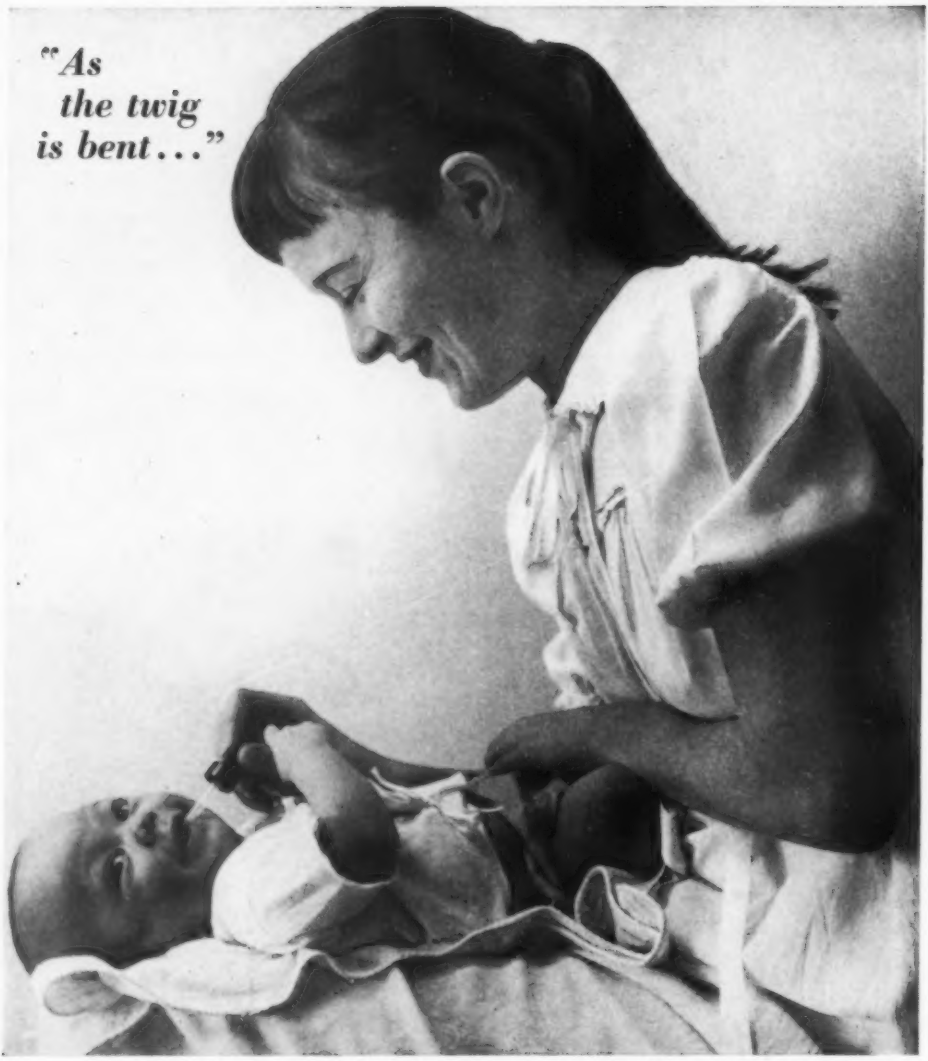
HOYT PHARMACEUTICAL CORP., Newton, Mass.

White's
Vitamin A and D
Ointment
clinically
well established
for its
emollient-protective
and
healing actions is
now also available
with 0.5 per cent
Prednisolone
for its
potent
anti-inflammatory
anti-pruritic
actions
and patient
comfort.



White's Vitamin A and D Ointment
with Prednisolone *0.5 per cent*
In 10 and 25 Gm. tubes on prescription.

White Laboratories, Inc.
Kenilworth, New Jersey



ZYMADROPS*

- Readily miscible with food and formula
- No refrigeration required
- Delightful new honey-lemon flavor

DOSAGE: *Infants and Children*—0.6 cc. daily or as directed by a physician. Zymadrops may be administered by dropping directly on the tongue or mixing with water, milk, fruit juice, or any other foods.

SUPPLIED: In 15, 30 and 60 cc. bottles.

Upjohn THE UPJOHN COMPANY, KALAMAZOO, MICHIGAN

*TRADEMARK, REG. U. S. PAT. OFF.—PEDIATRIC MULTIVITAMINS, UPJOHN

Check cough 8-12 hours

with a single dose

Rx TUSSIONEX®

A 'Strasionic' Antitussive • Dihydrocodeinone Resin—Phenyltoloxamine Resin

"STRASIONIC RELEASE" MAKES THE BIG DIFFERENCE

- **Permits Natural Discharge of Mucus**
- **Predictable Antitussive Action**
- **Minimum Amount of Narcotic**

TWO FORMS: Tussionex Thixaire™ Suspension • Tussionex Tablets

Each teaspoonful (5c.c.) or tablet provides 5 mg. dihydrocodeinone and 10 mg. phenyltoloxamine as resin complexes.

Dose: 1 teaspoonful or tablet q 12 h. Children under 1 year, ¼ teaspoonful q 12 h; 1-5 years, ½ teaspoonful q 12 h.

Rx only. Class B taxable narcotic.

Tussionex—made and marketed only by

STRASENBURGH LABORATORIES
ROCHESTER, N.Y., U.S.A.

Originators of 'Strasionic' (sustained ionic) Release

THE POPULAR NOSE DROP

IN PEDIATRIC CIRCLES

Tyzine® brand of tetrahydrozoline hydrochloride **PEDIATRIC NASAL DROPS***

LESS "FUSS" WHEN ADMINISTERED... AND FEWER ADMINISTRATIONS NEEDED

Extensive clinical experience with TYZINE shows minimal sting or burn on administration, no rebound congestion, and unusually well sustained effect—characteristics particularly suited to pediatric patients.

Note: As with certain other widely used nasal decongestants, overdosage may cause drowsiness or deep sleep in infants and young children: Keep out of hands of children of all ages.

Professional Information Available on Request.

*0.01% TYZINE

PFIZER LABORATORIES, Brooklyn 6, N. Y.
Division, Chas. Pfizer & Co., Inc.

Pfizer *Science for the world's well-being™*

for prompt and safe control of

nausea and vomiting

in children

THORAZINE* Syrup

and Suppositories

The use of 'Thorazine' in over 1,500,000 children since 1954 has shown that side effects other than mild sedation almost never occur in children.

SKF Smith Kline & French Laboratories

*T.M. Reg. U.S. Pat. Off. for chlorpromazine, S.K.F.

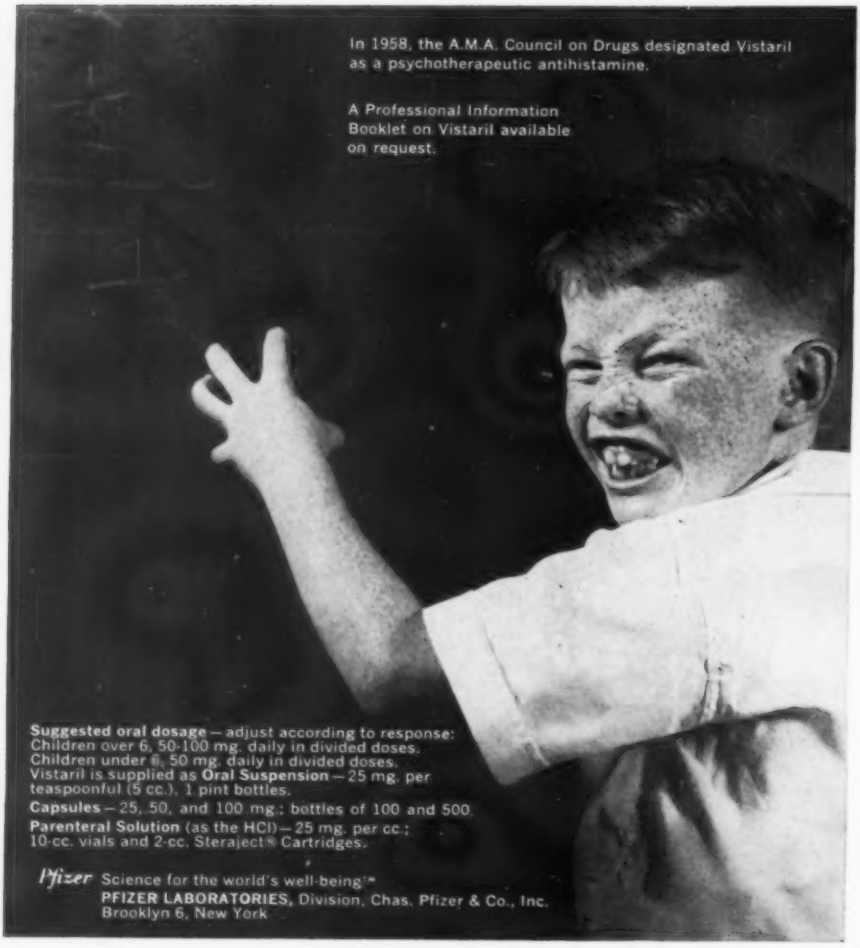
VISTARIL®

hydroxyzine pamoate

ORAL SUSPENSION

restores tranquility: relieves pruritus

Simultaneously, Vistaril releases tension and relieves itching. When the relief of severe apprehension is deemed necessary then Vistaril helps to tranquilize patients gently without impairing mental alertness.


In 1958, the A.M.A. Council on Drugs designated Vistaril as a psychotherapeutic antihistamine.
A Professional Information Booklet on Vistaril available on request.
Suggested oral dosage – adjust according to response:
Children over 6, 50-100 mg. daily in divided doses.
Children under 6, 50 mg. daily in divided doses.
Vistaril is supplied as Oral Suspension – 25 mg. per teaspoonful (5 cc.), 1 pint bottles.
Capsules – 25, 50, and 100 mg.; bottles of 100 and 500.
Parenteral Solution (as the HCl) – 25 mg. per cc.; 10-cc. vials and 2-cc. Steraject® Cartridges.
Pfizer Science for the world's well-being®
PFIZER LABORATORIES, Division, Chas. Pfizer & Co., Inc.
Brooklyn 6, New York

EVAPORATED OR POWDERED, Meyenberg Goat Milk is nutritionally equal to cow's milk in carbohydrates, protein and fat. And since the offending antigen in cow's milk is usually lactalbumin (a species protein), goat milk has often proved a successful substitute for cow's milk. Therefore, the infant is not deprived of the irreplaceable values of milk, as may occur when synthetic milk formulas are fed. *Recent clinical findings indicate there are nutritive values in natural animal milk that are lacking in synthetic preparations.**

In addition, Meyenberg Goat Milk is free of crude fibers and other extraneous material which may cause digestive upset. Gastrointestinal disturbances with abnormal stools, diarrhea, sore buttocks, cramping and occasional vomiting have been reported* following the ingestion of soy preparations. Thus, for infants allergic to cow's milk, prescribe Meyenberg Goat Milk *first* – either Evaporated or Powdered.

Always prescribe Meyenberg – the standard for highest, most dependable quality since 1934.

FULL-SIZE TRIAL CAN ON REQUEST.
Powdered in 14 oz. cans, evaporated in 14 fl. oz. cans.

JACKSON-MITCHELL *Pharmaceuticals, Inc.*
10401-D Virginia Ave., Culver City, Calif.

*FRIES, J. H., MILK ALLERGY – DIAGNOSTIC ASPECTS AND THE ROLE OF MILK SUBSTITUTES, J.A.M.A., NOV. 23, 1957.

UNIQUE VITAMIN SUPPLEMENT

NEW VIGRAN CHEWABLES

SQUIBB MULTIPLE VITAMIN SOFT TABLETS

fruit-punch flavored tablets that will actually "melt in the mouth"

can be chewed like candy

can be crushed and sprinkled on cereal or other food

can be dissolved in water, juice or milk

can be sucked and will dissolve like a lozenge

can be easily swallowed (small tablet size)

VIGRAN CHEWABLES *taste like candy,* but contain *no ingredients harmful to teeth.* Important, too, is that VIGRAN CHEWABLES *dissolve easily* in the mouth and *smell good.* And VIGRAN CHEWABLES provide at least 125% of the minimum daily requirements for vitamins A, D, B_1, B_2, niacinamide and C, and significant amounts of other essential vitamins.

Each VIGRAN CHEWABLE tablet contains:

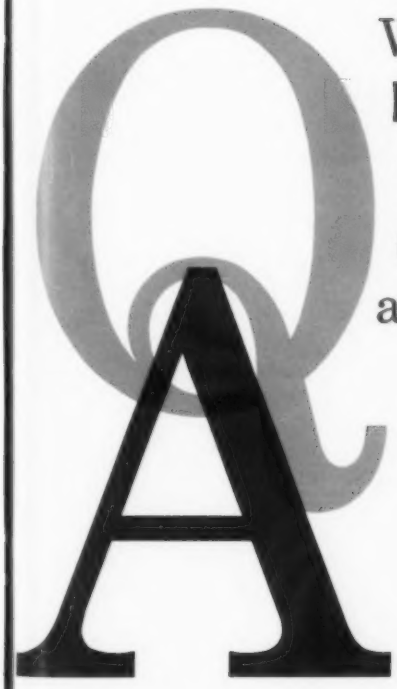
Vitamin A	5,000 U.S.P. units
Vitamin D	1,000 U.S.P. units
Vitamin C	75 mg.
Vitamin B_1	3 mg.
Vitamin B_2	3 mg.
Vitamin B_6	2 mg.
Niacinamide	25 mg.
Calcium Pantothenate	3 mg.
Vitamin B_{12}	5 mcg.

Available in Rx-size bottles of 30 and 90.

SQUIBB

Squibb Quality—the Priceless Ingredient

'Vigran'® is a Squibb trademark



Why should I use **KANTREX®** Injection* when there are so many other antibiotics available?

Because KANTREX Injection is bactericidal to a wide variety of organisms, including many that are highly resistant to the other antibiotics[3,4,10,12,13,17,18,20,21,23,24,25,27,30,33,35,37]

—organisms such as *Staph. aureus, Staph. albus, A. aerogenes, E. coli, H. pertussis, K. pneumoniae, Neisseria* sp., *Shigella, Salmonella* and many strains of *B. proteus.*

Q *But if I use* KANTREX *Injection, won't that help make bacteria resistant to it also?*

Next page, please . . . . . .

* Kanamycin sulfate injection (Bristol)

Q *But if I use* KANTREX *Injection, won't that help make bacteria resistant to it also?*

A A very good question, but it is reassuring to note that in almost two years of clinical use of KANTREX for the treatment of infections for which it is recommended, the emergence of KANTREX-resistant bacterial populations has not been a problem.

Q *My impression is that* KANTREX *is just another neomycin. Isn't that so?*

A Indeed not. The only thing KANTREX and neomycin have in common is a similar antimicrobial spectrum. Otherwise, they're very different: they have different chemical structures; the toxicity of KANTREX is "much less than that of neomycin"[14]; and clinically, KANTREX Injection is practical for systemic administration routinely, while neomycin is not.

Q *You mean that* KANTREX *Injection doesn't have the nephrotoxicity of neomycin?*

A Precisely. It's true that when KANTREX Injection is used, urinary casts – even slight albuminuria or microscopic hematuria – may appear, especially in poorly hydrated patients, but this does not reflect any progressive damage to the kidneys. These signs promptly disappear on adequate hydration or termination of therapy.

Q *Then why do you recommend reduced dosage in patients with renal impairment?*

A Because renal impairment causes an excessive accumulation of KANTREX in the blood and tissues, when usual doses are administered. Since KANTREX Injection is excreted entirely by the kidneys, renal impairment leads

to unnecessarily high and prolonged blood levels; and such excessive concentrations increase the risk of ototoxicity.

Q *Is that why we see reports of patients developing hearing loss during* KANTREX *Injection therapy?*

A Yes. A study of the few reported cases in which patients have suffered impaired hearing will show that in every instance they had pre-existing or concurrent renal impairment, yet received usual or excessive doses of KANTREX Injection. Dosage recommendations for KANTREX Injection emphasize that in patients with renal dysfunction, adequate serum levels can be achieved with a fraction of the dose suggested for patients with normal kidney function – with minimal risk of ototoxicity.

Q *Since urinary tract infections are often accompanied by renal impairment, does that mean I shouldn't use* KANTREX *Injection in such conditions?*

A Not at all. With proper precautions, KANTREX Injection is an excellent drug for the treatment of urinary tract infections, especially those due to *Proteus*, *A. aerogenes* and *E. coli*, even when renal impairment is present.

Q *What are the "proper precautions" in a patient with impaired renal function?*

A The package literature covers them in detail. First, the daily dose should be reduced in such a patient. Then, if he is going to receive KANTREX Injection for 7 days or more, a pre-treatment audiogram should be done, and it should be repeated at appropriate intervals during therapy. If tinnitus or subjective hearing loss develops, or if followup audiograms show significant loss of high frequency response, KANTREX therapy should be discontinued. However, therapy for 7 days or more

is seldom required because the clinical response to KANTREX Injection is so rapid.

Q *Why do you put so much emphasis on* KANTREX'S *"rapid action"? Every antibiotic I've heard about is supposed to be "rapid acting."*

A There is such an abundance of clinical evidence about "rapid acting" that it takes KANTREX Injection out of the "supposed-to" class.[1,2,3,7,8,9,11,15,16,19,21,22,26,29,32,33] Remember, the effectiveness of KANTREX Injection therapy can usually be appraised in 24 to 36 hours. That's definite evidence of rapid action. In fact, one group of investigators reported that "the rapidity with which bacteria are killed by this agent is reflected by the promptness of the clinical response."[29]

Q *Does* KANTREX *Injection cause blood dyscrasias?*

A In extensive clinical and toxicity studies by numerous investigators, as well as almost two years of general use, not a single instance of such toxicity has been reported.

Q *Can I administer* KANTREX *Injection in any other way than by the intramuscular route?*

A Yes. While it's usually given intramuscularly, other routes are practicable: intravenous, intraperitoneal, by aerosol, and as an irrigating solution. Complete instructions are included in the package insert.

Q *So you think I ought to use* KANTREX *Injection as my first choice antibiotic in staph and gram-negative infections?*

A Yes – because all evidence to date indicates that it is bactericidal against a wide range of organisms…rapid acting…does not encourage development of bacterial resistance…is well tolerated in specified dosage…and has not caused any blood dyscrasias.

KANTREX® CAPSULES

for local gastrointestinal therapy... not for systemic infections

Q *Why can't I use* KANTREX *Capsules for systemic medication?*

A Because there is only negligible absorption of KANTREX from the gastrointestinal tract.[3,5,6,8,28,34] Thus, capsules cannot provide effective blood levels.

Q *Then what are* KANTREX *Capsules used for?*

A Preoperative bowel sterilization, and local treatment of intestinal infections due to kanamycin-sensitive organisms.

Q *I've been using neomycin for preoperative bowel sterilization. Why should I switch to* KANTREX *Capsules?*

A Because KANTREX has been rated as "superior to neomycin" for this purpose.[6] It provides rapid and satisfactory control of coliforms, clostridia, staphylococci and streptococci; yeasts do not proliferate; stool concentrations of the drug are exceptionally high; and nausea, vomiting or intestinal irritation have not been observed.[5,6]

Q *What advantages do* KANTREX *Capsules offer me in the treatment of intestinal infections?*

A A high degree of effectiveness against most of the pathogens responsible for such infections: *Salmonella, Shigella, Staph. aureus, E. coli* and *Endamoeba histolytica.* Moreover, their use has been "remarkably free of any side effects."[31]

KANTREX®

INJECTION KANAMYCIN SULFATE INJECTION

INDICATIONS

Infections due to kanamycin-sensitive organisms, particularly staph or "gram-negatives": genito-urinary infections; skin, soft tissue and post-surgical infections; respiratory tract infections; septicemia and bacteremia; osteomyelitis and periostitis.

DOSAGE: INTRAMUSCULAR ROUTE

Recommended daily dose is 15 mg. per kg. of body weight, in 2 to 4 divided doses.

For intramuscular administration, KANTREX Injection should be injected deeply into the upper outer quadrant of the gluteal muscle.

TOXICITY

When the recommended precautions are followed, the incidence of toxic reactions to KANTREX is low. In well hydrated patients under 45 years of age with normal kidney function, receiving a total dose of 20 Gm. or less of KANTREX, the risk of ototoxic reactions is negligible.

In patients with renal disease and impaired renal function, the daily dose of KANTREX should be reduced in proportion to the degree of impairment to avoid accumulation of the drug in serum and tissues, thus minimizing the possibility of ototoxicity. In such patients, if therapy is expected to last 7 days or more, audiograms should be obtained prior to and during treatment. KANTREX therapy should be stopped if tinnitus or subjective hearing loss develops, or if audiograms show significant loss of high frequency response.

OTHER ROUTES OF ADMINISTRATION

KANTREX should be used by intravenous infusion only when the intramuscular route is impracticable. KANTREX can also be employed for intraperitoneal use, aerosol treatment, and as an irrigating solution. See package insert for directions.

PRECAUTIONS

Use of antibiotics may occasionally result in overgrowth of non-sensitive organisms. If superinfection appears during therapy, appropriate measures should be taken.

SUPPLY

Available in rubber-capped vials as a ready-to-use sterile aqueous solution in two concentrations (stable at room temperature indefinitely):

KANTREX Injection, 0.5 Gm. kanamycin (as sulfate) in 2 ml. volume.
KANTREX Injection, 1.0 Gm. kanamycin (as sulfate) in 3 ml. volume.

CAPSULES (for local gastrointestinal therapy; not for systemic medication)

INDICATIONS AND DOSAGE

For preoperative bowel sterilization: 1.0 Gm. (2 capsules) every hour for 4 hours, followed by 1.0 Gm. (2 capsules) every 6 hours for 36 to 72 hours.

For intestinal infections: Adults: 3.0 to 4.0 Gm. (6 to 8 capsules) per day in divided doses for 5 to 7 days. Infants and children: 50 mg. per kg. per day in 4 to 6 divided doses for 5 to 7 days.

PRECAUTION

Preoperative use of KANTREX Capsules is contraindicated in the presence of intestinal obstruction. Although only negligible amounts of KANTREX are absorbed through intact intestinal mucosa, the possibility of increased absorption from ulcerated or denuded areas should be considered.

SUPPLY

KANTREX Capsules, 0.5 Gm. kanamycin (as sulfate), bottles of 20 and 100.

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Bristol LABORATORIES INC. • Syracuse, New York

B.H., age 15. Neurodermatitis with secondary pyoderma of 6 months' duration.

Photographs courtesy of Charles M. Howell, Jr., M.D., Bowman Gray School of Medicine, Wake Forest College, Winston-Salem, N. C.

infected
oozing
ulcerous
itching
inflammatory

complete control of skin conditions

After Triburon-HC Ointment for 16 days.

NEW Triburon-HC OINTMENT
(WITH HYDROCORTISONE)

the anti-inflammatory, antipruritic benefits of hydrocortisone combined with the microbicidal action of Triburon

NEW TRIBURON OINTMENT

wide-spectrum topical microbicide

In 43 of 52 dermatologic patients – mostly children – Triburon proved to be "...an effective agent..."[1] for a gamut of eczematous conditions; for primary and secondary pyodermas – despite previous antibiotic failure. "Within 1 week... prompt improvement with diminished crusting and clearing of the pustules and exudations..."[2] appeared in a 19-month-old child previously treated unsuccessfully for 2½ months with various methods.

- *active even against antibiotic-resistant skin pathogens*
- *avoids sensitization to systemically used antibiotics*
- *nonirritating*
- *nonstaining*
- *wide safety margin, even in the event of accidental ingestion*

Triburon-HC Ointment when the anti-inflammatory and antipruritic action of a steroid is desirable.

Triburon Ointment 0.1% for the prevention and treatment of skin and other surface infections such as pyodermas, furunculosis, infected dermatoses, pustular folliculitis, and infected burns. (Triburon-impregnated dressings can be autoclaved.)

Available: Ointment, containing 0.1 per cent Triburon in 1-oz tubes and 1-lb jars. Ointment, containing 0.1 per cent Triburon plus 0.5 per cent hydrocortisone, in 5-Gm and 20-Gm tubes.

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1. S. Bielinski, J. M. Fox and A. B. Falk, Ann. New York Acad. Sc., 82:(1), 141-144, Sept. 1, 1959.

2. P. L. Williams, ibid., pp. 135-140.

TRIBURON® Chloride – brand of triclobisonium chloride – N,N'-bis [1-methyl-3-(2,2,6-trimethylcyclohexyl)propyl]-N,N'-dimethyl-1,6-hexanediamine bis (methochloride) ROCHE®

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NEW LIQUID AND POWDERED

because renal solute load and water requirements are held within normal limits by a physiologic protein/electrolyte pattern comparable to that of breast milk. Particularly important during periods of febrile illness, diarrhea, and in hot weather. Easy for mothers . . . just add water

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AND FOR THOSE WHO CAN'T "TAKE" MILK...*MULL-SOY*®

Patient expresses confidence in doctor's cough medicine

AN EXPRESSION OF CONFIDENCE in your therapeutic ability may be expected when you prescribe Pyribenzamine Expectorant for cough in children. A combination of 3 active agents, Pyribenzamine Expectorant with Ephedrine relieves congestion, makes breathing easier, promotes productive expectoration. And the cherry flavor is usually quite acceptable to pediatric tastes.

DOSAGE: ½ to 1 teaspoon every 3 or 4 hours.

SUPPLIED: Expectorant with Ephedrine, containing 30 mg. Pyribenzamine citrate 10 mg. ephedrine sulfate and 80 mg. ammonium chloride per 4-ml. teaspoon.

ALSO AVAILABLE: Pyribenzamine Expectorant with Codeine and Ephedrine, same formula plus 8 mg. codeine phosphate (exempt narcotic).

PYRIBENZAMINE® citrate (tripelennamine citrate CIBA)

2626MB

Pyribenzamine® Expectorant with EPHEDRINE

CIBA
SUMMIT, N. J.

"no intolerance to molybdenized iron"[1]

...in a study of anemic premature infants—but 20% were intolerant to other iron salts. Mol-Iron is not just an ordinary iron salt—It is a specially processed co-precipitated complex of ferrous and molybdenum salts. Molybdenum is reported to protect the ferrous iron from oxidation to the more irritant ferric form...hence, the unmatched tolerance of Mol-Iron.[2*]

Mol-Iron® liquid & drops...

(Molybdenized-Ferrous Complex)

for therapy and prophylaxis of iron deficiency in children and infants

Mol-Iron Liquid: 12 fl. oz. bottles, each tspfl. contains 195 mg. ferrous sulfate and 3 mg. molybdenum oxide. **Mol-Iron Drops:** 15 cc. and 50 cc. bottles with dropper, each cc. contains 125 mg. ferrous sulfate and 2 mg. molybdenum oxide.

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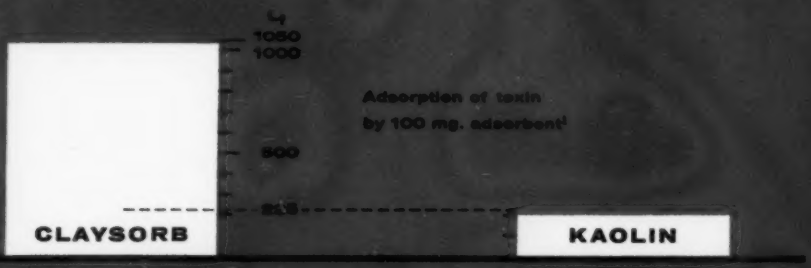
*COMPLETE BIBLIOGRAPHY AVAILABLE ON REQUEST.

WHITE LABORATORIES, INC. · KENILWORTH, NEW JERSEY

in diarrhea . . .

adsorptive power



CLAYSORB is 5 times as adsorptive as kaolin

When you prescribe POLYMAGMA or POLYMAGMA Plain to control diarrhea, you are prescribing adsorptive superiority. Both preparations contain Claysorb—a new intestinal adsorbent whose superiority over kaolin has been demonstrated in exhaustive studies.[1,2,3]

For *bacterial* diarrhea, POLYMAGMA is bactericidal to many intestinal pathogens. It is soothing and protective to the irritated mucosa. It aids in the restoration of normal intestinal function. Highly effective, highly palatable.

For *nonbacterial* diarrhea, POLYMAGMA Plain—same formula but without antibiotics.

1. Barr, M., and Arnista, E.S.: J. Am. Pharm. A. (Scient. Ed.) *46*:493 (Aug.) 1957. 2. Barr, M., and Arnista, E.S.: *Ibid. 46*:486 (Aug.) 1957. 3. Barr, M.: *Ibid. 46*:490 (Aug.) 1957.

Polymagma®

Dihydrostreptomycin Sulfate, Polymyxin B Sulfate, and Pectin with Claysorb* (Activated Attapulgite, Wyeth) in Alumina Gel

Wyeth®
Philadelphia 1, Pa.

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This advertisement conforms to the Code for Advertising of the Physicians' Council for Information on Child Health

gives as good as she gets

VIFORT®

(Aqueous Polyvitamin)

DROPS

- completely water-soluble... including vitamins A and D
- 3 to 5 times better absorbed, utilized, and stored than from oily media
- deliciously orange-flavored... a treat for infants and growing children
- backed by years of clinical study and pediatric application

Dosage: 0.3 to 0.6 cc. daily; may be placed directly on tongue or taken in fruit juices or milk.

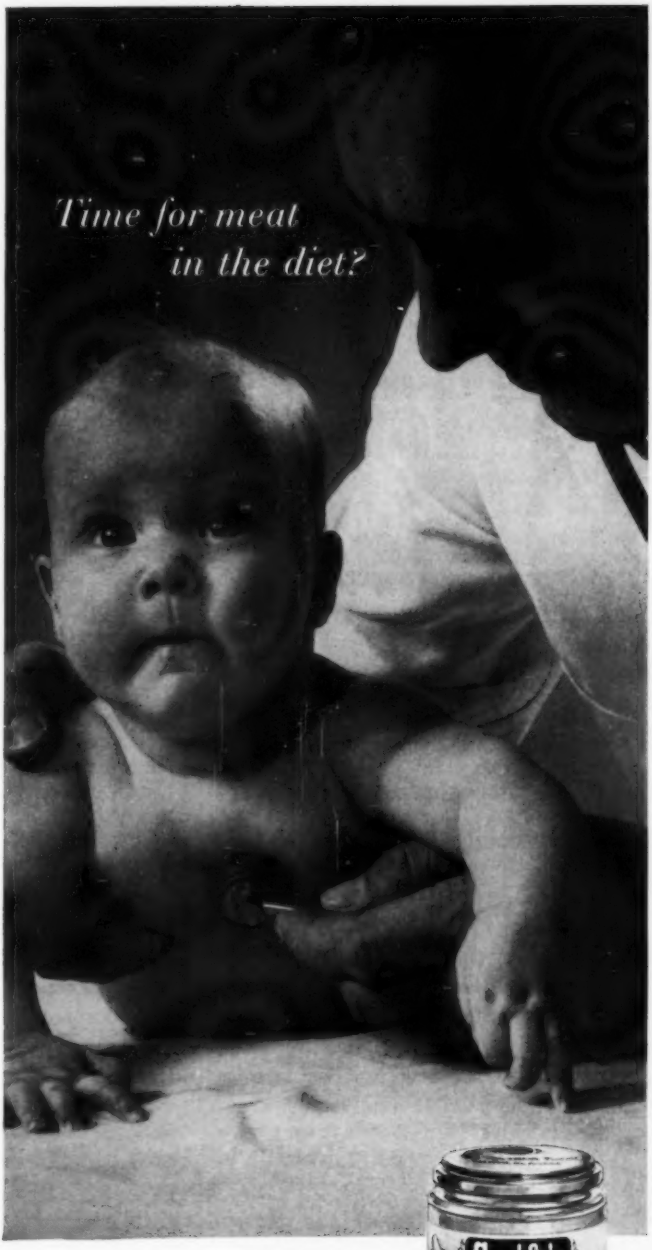
Supplied: bottles of 15, 30, and 60 cc. with graduated dropper.

Also available: VIFORT Capsules, bottles of 30 and 100.

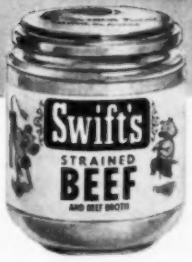
Samples? Literature? Write–

ENDO LABORATORIES INC. Richmond Hill 18, New York

Endo®



Nine 100% Meats...also
6 High Meat Dinners



...then it's time to trust SWIFT ...the meat specialist!

To help your little patients enjoy the maximum of meat's many benefits, Swift prepares this vital growth food in its most delicious and easily assimilated form.

All Swift's skill goes into selecting extra lean meat with its higher protein content . . . processing carefully to retain nutritional values . . . straining the meat finer. And assuring flavors so appetizing they aid in establishing sound eating habits early.

Only Swift *specializes* in delicious, nourishing meats and meat dishes for babies.

the two most trusted words in meat.

Swift's Premium

OUR 105TH YEAR

PSYCHONORMALIZING

Deaner®

deanol acetamidobenzoate

in the adjustment of School-Age Problem Children

when intelligence is masked by behavior problems, in the absence of organic cause

- Improves scholastic performance...
- Lengthens attention span...
- Improves social adaptability...
- Decreases irritability

Dosage

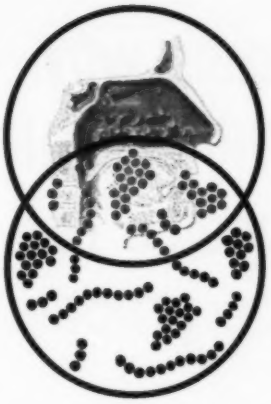
75 mg. (3 tablets) in the morning is the recommended starting dose. After two weeks, or whenever satisfactory improvement has occurred, a reduced dose may maintain this improvement in some cases; however, optimal response has been reported in most children on maintenance doses ranging from 75 mg. (3 tablets) to 150 mg. (6 tablets) per day.

Contraindications

'Deaner' therapy is contraindicated only in grand mal epilepsy and in mixed epilepsy with a grand mal component.

Deaner may be given with safety to patients with previous or current liver disease, kidney disease, or infectious diseases.

Riker Northridge, California



in pediatric patients

when upper respiratory congestion

is complicated by bacterial invaders

Trisulfaminic Suspension provides logical therapy

- for the child ill with congestion and infection of the upper respiratory tract, as in purulent rhinitis, sinusitis, tonsillitis and otitis media, when caused by sulfa-susceptible bacteria:
- because secondary invasion by such bacteria so frequently follows the common cold.[1]

the reasons for combining Triaminic with triple sulfas

Triaminic and triple sulfas are not only pharmacologically *compatible*, they are a therapeutically *logical* combination for upper respiratory infections: Triaminic for effective decongestant relief from rhinitis, rhinorrhea and sinusitis;[2] triple sulfas for well-established antibacterial action.

The advantages of Trisulfaminic in upper respiratory infections include: proved effectiveness; safety; economy; ease of administration; less likelihood of sensitivity reactions;[3] compatible with antibiotics and other antibacterial therapy. Available also as Trisulfaminic Tablets.

Trisulfaminic® *Suspension*

TRIAMINIC WITH TRIPLE SULFAS

highly acceptable to patient and parent—palatable, effective, convenient

Each 5 ml. teaspoonful of Trisulfaminic Suspension or each Tablet provides:

TRIAMINIC®	25 mg.
(phenylpropanolamine HCl	12.5 mg.
pheniramine maleate	6.25 mg.
pyrilamine maleate	6.25 mg.)
Trisulfapyrimidines, U.S.P.	0.5 Gm.

Dosage: Children 8-12 years old—2 tsp. or tablets initially, followed by 1 tsp. or tablet every 6 hours, until the patient has been afebrile 3 days. Children under 8—initially, ½ tsp./10 lb. body weight, to a maximum of 2 tsp., then about ½ of this dose every 6 hours. Adults—2 to 4 tsp. or tablets initially, followed by 2 tsp. or tablets every 4 to 6 hours.

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SMITH-DORSEY • a division of The Wander Company • Lincoln, Nebraska

3 outstanding reasons why ST. JOSEPH ASPIRIN FOR CHILDREN is an aspirin of choice in pediatric practice

1. It has the most widely accepted dosage

Each of these specialized aspirin tablets contains 1¼ grains of highest quality aspirin—the dosage most widely accepted by doctors.

2. It affords exceptional palatability

The pleasant orange flavor and smooth, creamy texture make St. Joseph Aspirin For Children an elegant pharmaceutical that children readily accept without fuss or fretting.

3. It provides a special safety cap

The new plastic Safety Cap on St. Joseph Aspirin For Children cannot be twisted off—pressure against its sides makes it hold even tighter. It can be removed only by pressure applied at just the right point according to the directions on the bottle through narrow vertical grooves in the bottle rim.

In Canada this product is available under the trade name of ST. JOSEPH BEBETINE FOR CHILDREN.

FOR THESE REASONS—as well as because aspirin is the most widely used drug in the world, and one of the safest and most effective drugs in the entire range of medicine—St. Joseph Aspirin For Children is a medication of choice whenever salicylate therapy is indicated in infancy and childhood. You can prescribe and recommend this specialized aspirin tablet with complete confidence.

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DESITIN®
OINTMENT

in preventing and healing **diaper rash**

- **blocks** irritation due to urine and excrement
- **fights** ammonia and rash-producing bacteria
- **counters** and clears up chafing, rawness, excoriation

DESITIN OINTMENT the pioneer soothing, protective healing external cod liver oil therapy.

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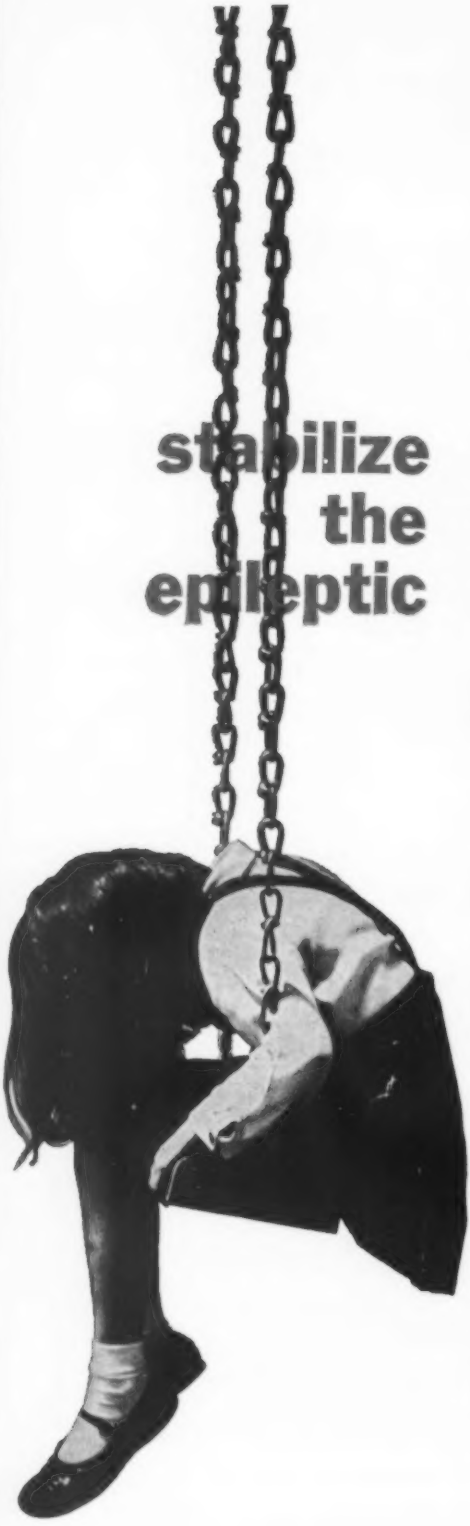

stabilize the epileptic

Better control of seizures and better understanding by parents before a child starts school help a great deal to establish a stable, normal outlook in the epileptic.

Highly effective: In most types of seizures, especially major motor seizures, **MEBARAL** is one of the best-tolerated anticonvulsants for children. This antiepileptic does not tend to lower learning capacity.

Unsurpassed safety: Mebaral is not likely to cause hyperactivity in young children. Toxic reactions or ill effects from it are rare.

MEBROIN®, combining Mebaral and diphenylhydantoin, is synergistic—and side effects are infrequent. Each relatively tasteless Mebroin tablet contains 90 mg. Mebaral and 60 mg. diphenylhydantoin. Mebroin brings maximal control of seizures with minimal toxicity.

Mebaral dosage: CHILDREN under 5 years, from ¼ to ½ grain three or four times daily; over 5 years, from ½ to 1 grain three or four times daily. ADULTS, from 6 to 9 grains daily.

Mebroin dosage: CHILDREN under 6 years, ½ tablet once or twice daily; over 6 years, 1 tablet two or three times daily. ADULTS, 1 or 2 tablets three times daily (average dosage).

For epilepsy at any age

MEBARAL®

Supplied: **MEBARAL** tasteless tablets of 200 mg. (3 grains), 100 mg. (1½ grains), 50 mg. (¾ grain), 32 mg. (½ grain). Bottles of 100.

MEBROIN virtually tasteless tablets. Bottles of 100.

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DEMONSTRATED HEMATOLOGIC RESPONSE*

SIMILAC®
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12 mg of ferrous iron per quart of formula

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Marsh, A.K., et al.: Pediatrics *24*:404, 1959.

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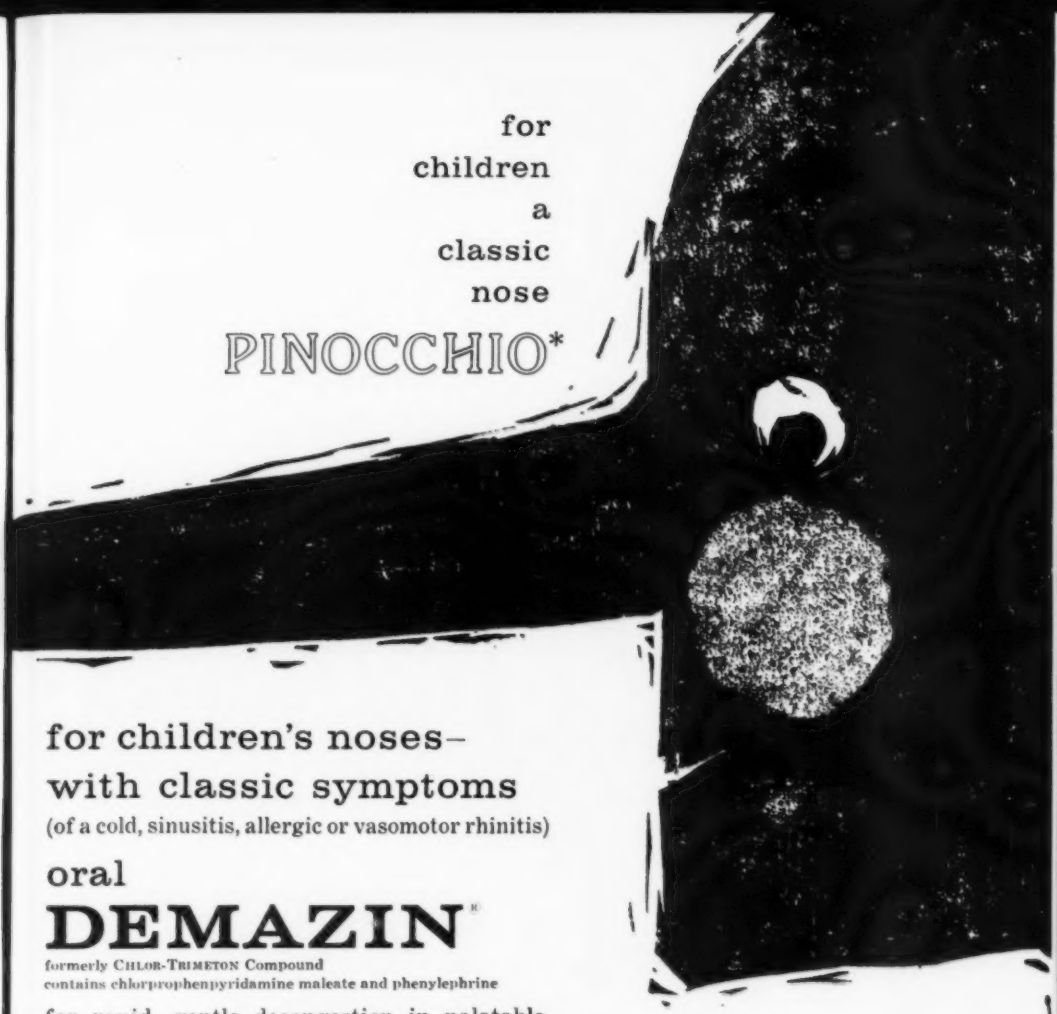

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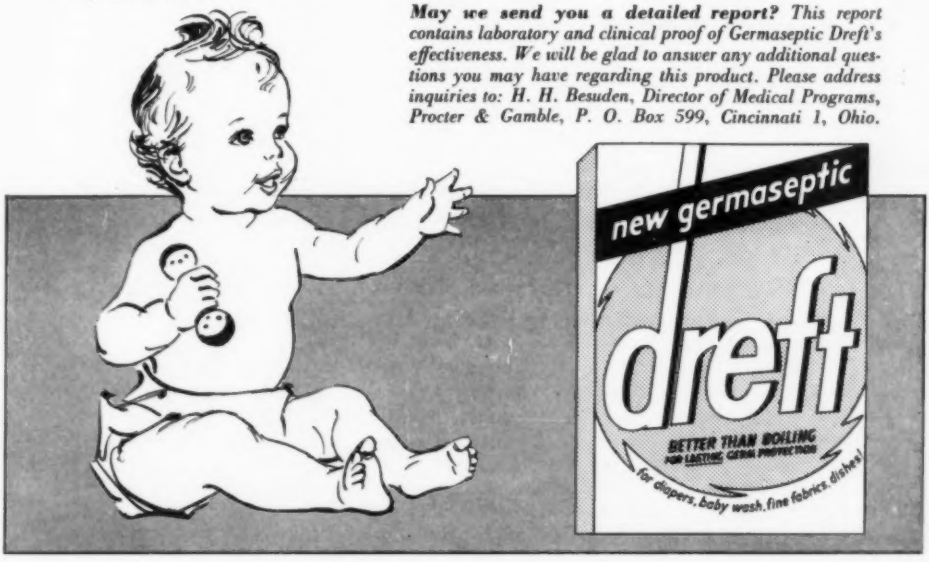

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IMPORTANT: Do not dilute or take other fluids immediately before or after each dose.

Supplied: Bottles of 3 fl.oz. and 16 fl.oz.

1. Bradley, J. E., et al.: J. Pediat. 38:41, 1951.
2. Bradley, J. E.: Mod. Med. 20:71, No. 20, 1952.
3. Tebrock, H. E., and Fisher, M. M.: M. Times 82:271, 1954.

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Kretschmer, N.: Development of Enzyme Activities in Fetal, Neonatal and Infantile Life.

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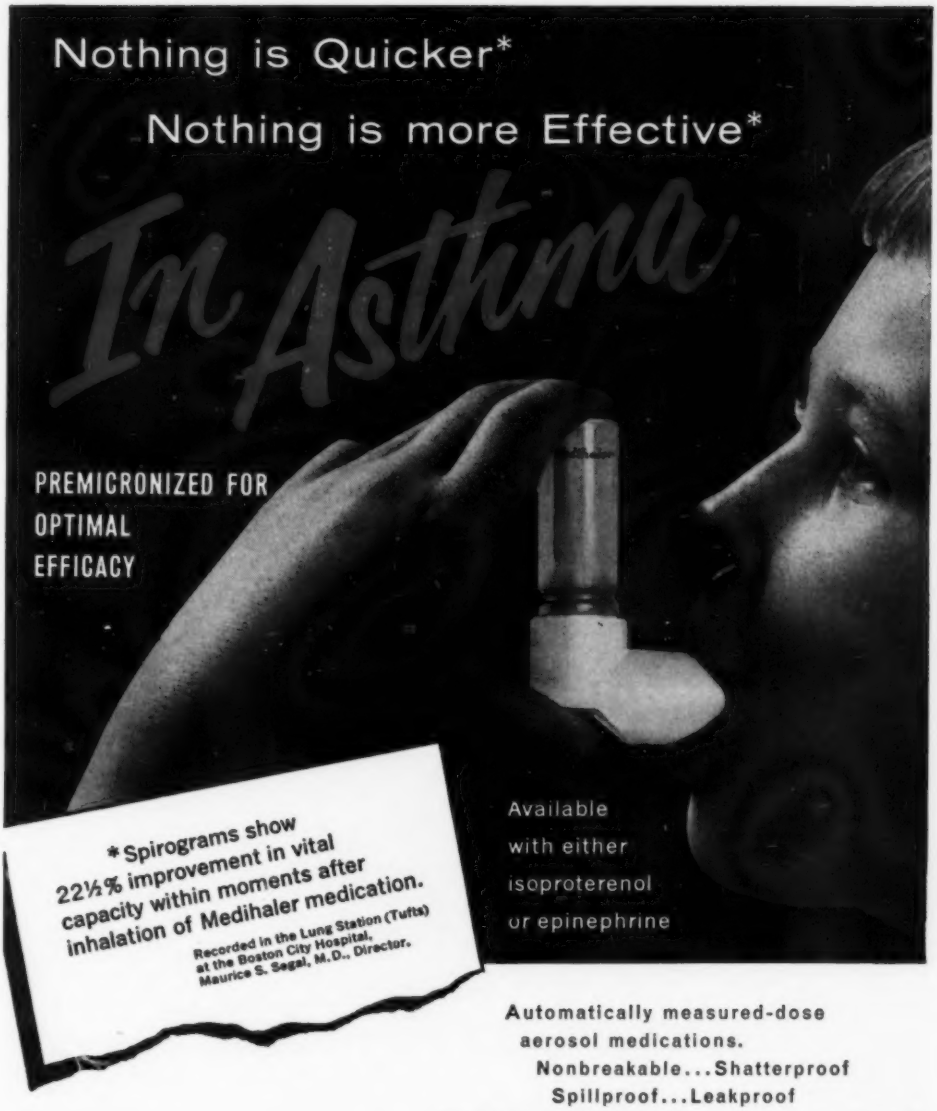
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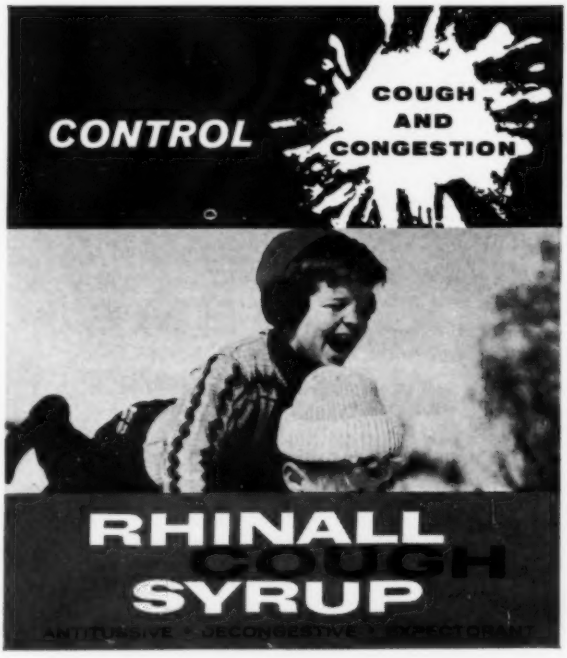

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makes cough more productive

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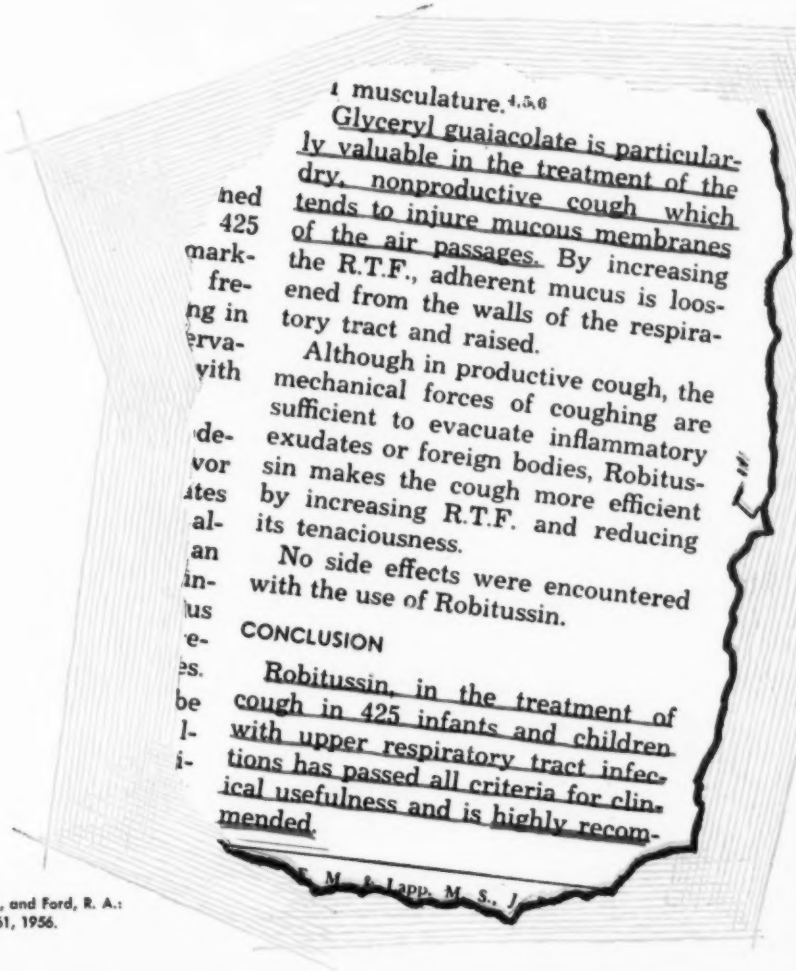
"Highly recommended"[1]

for cough relief in infants and children



musculature.[4,5,6]

Glyceryl guaiacolate is particularly valuable in the treatment of the dry, nonproductive cough which tends to injure mucous membranes of the air passages. By increasing the R.T.F., adherent mucus is loosened from the walls of the respiratory tract and raised.

Although in productive cough, the mechanical forces of coughing are sufficient to evacuate inflammatory exudates or foreign bodies, Robitussin makes the cough more efficient by increasing R.T.F. and reducing its tenaciousness.

No side effects were encountered with the use of Robitussin.

CONCLUSION

Robitussin, in the treatment of cough in 425 infants and children with upper respiratory tract infections has passed all criteria for clinical usefulness and is highly recommended.

[1] Blanchard, K., and Ford, R. A.: Clin. Med. 3:961, 1956.

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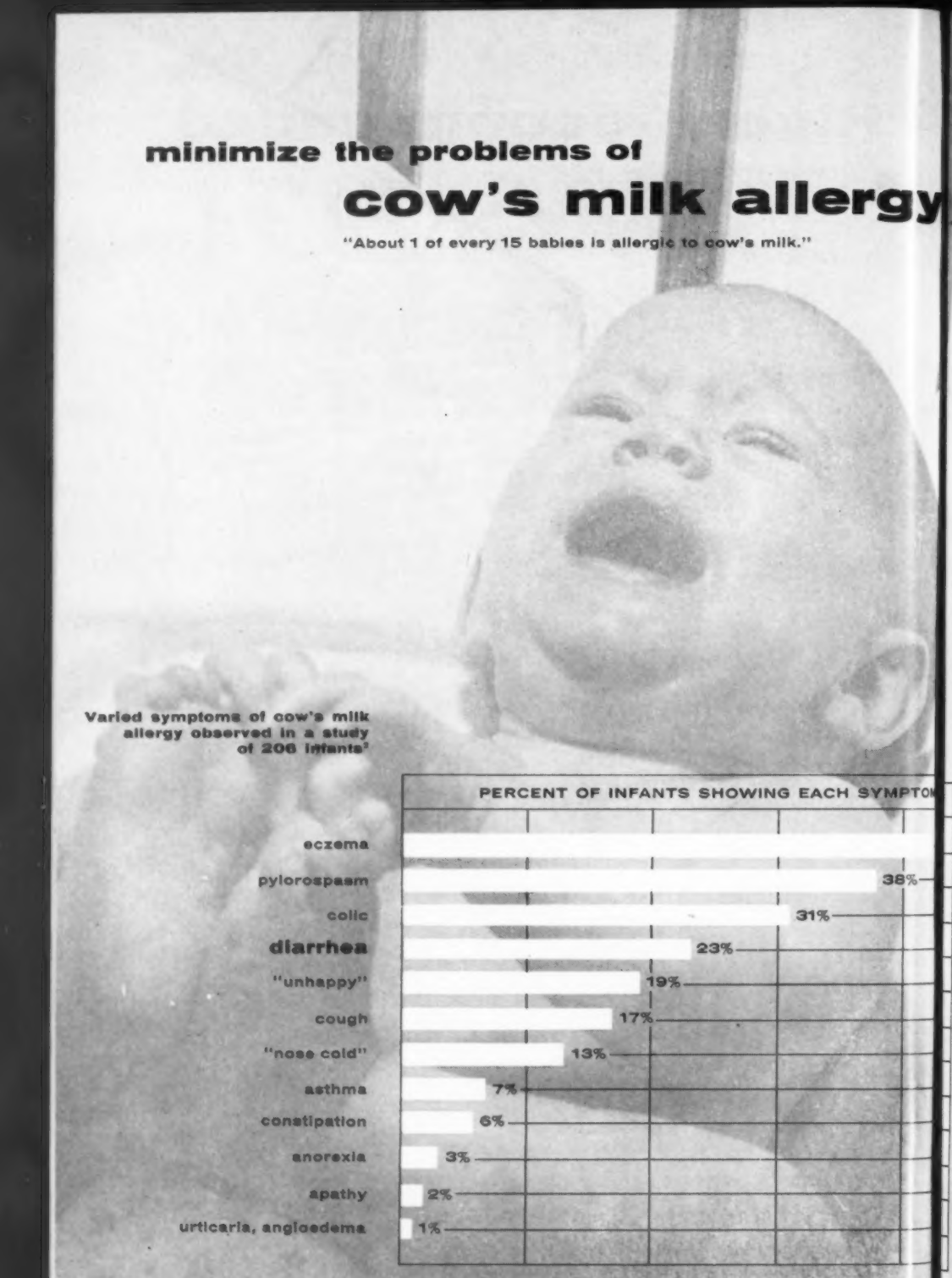

All of the listed symptoms were relieved by substituting soya formula for cow's milk formulas

specify **Sobee**

relieve **Diarrhea** *and other symptoms in the milk-allergic infant . . .*

for treatment

In a study[3] of 24 infants allergic to cow's milk, it was reported that when the infants were fed Sobee, "Weight gain was satisfactory in all cases during the periods of observation. For the most part stools were of normal colour and were soft in consistency . . . in contra-distinction to the very loose stools that resulted when many of the patients received cow's milk."

Sobee was fed to 102 infants with cow's milk allergy: "The stools were of a normal pattern, non-staining, non-loose, and non-malodorous."[4]

for prevention

When allergic tendencies exist in the parents or siblings, it is prudent to start the "potentially allergic"[5] newborn on a milk substitute, such as Sobee.

for diagnosis

When cow's milk allergy was suspected from the presenting symptoms, it was found that "it was simpler and easier to remove cow's milk from the diet for a twenty-four to forty-eight hour trial period and substitute soybean milk than start an allergic study . . ."[2]

references:

1. Clein, N. W.: Modern Med. 24: 69-75 (Feb.) 1956. 2. Clein, N. W.: Pediat. Clin. North America, Nov., 1954, pp. 949-962. 3 Collins-Williams, C.: Canad. M.A.J. 75: 934 (Dec. 1) 1956. 4. Kane, S.: Am. Pract. & Digest. Treat. 8: 65 (Jan.) 1957. 5. Glaser, J.: Allergy in Childhood, Springfield, Ill., Charles C Thomas, 1956, chap. 67, p. 494.

to relieve milk-allergy symptoms while maintaining sound nutrition . . . specify

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liquid • "instant" powder

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Symbol of service in medicine

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WILLIAM B. SHERMAN, M.D., Associate Clinical Professor of Medicine, Columbia University College of Physicians and Surgeons; Associate Attending Physician, Presbyterian Hospital; Attending Physician, Roosevelt Hospital, New York, New York; and **WALTER R. KESSLER, M.D., Ph.D.**, Instructor in Pediatrics, Columbia University College of Physicians and Surgeons; Assistant Pediatrician, Babies Hospital; Assistant Attending Physician, Roosevelt Hospital, New York, New York.

1957, 296 pages, 6¾" x 9¾", illustrated. Price $9.25

Here is practical aid in the diagnosis and treatment of infants and children suffering from allergic diseases. A certain amount of basic scientific background is included for the intelligent use by general practitioners and pediatricians without special training in allergy.

It presents in detail the views and methods which have been found most useful in actual practice. When controversial problems are discussed the authors indicate the differences of opinion and differentiate fact from theory. However, the desire to keep the book simple and practical does not permit detailed and impartial presentation of all points of view on controversial problems. Attention is focused on those diseases in which allergic methods of diagnosis and treatment have proved of real, practical value.

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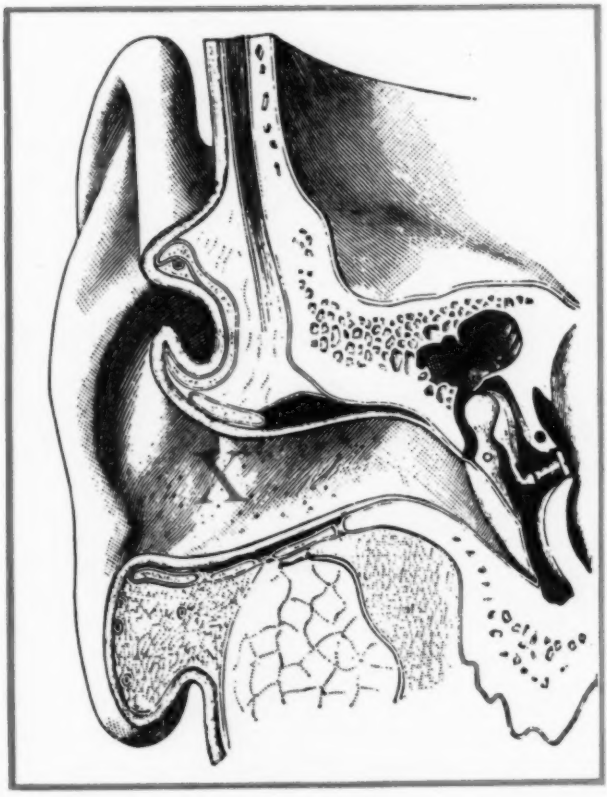

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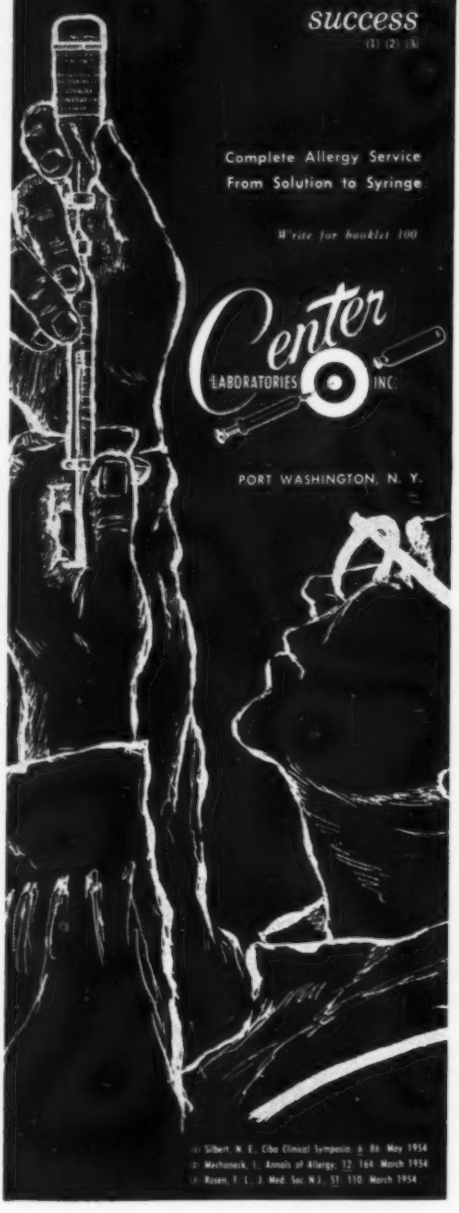

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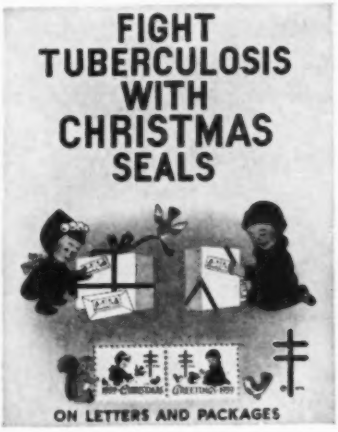

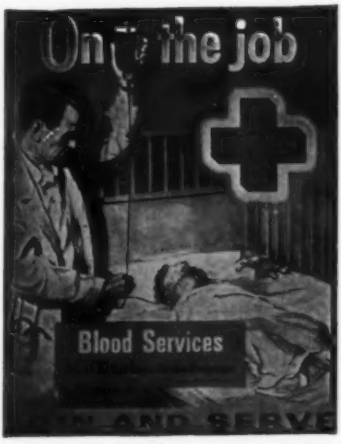

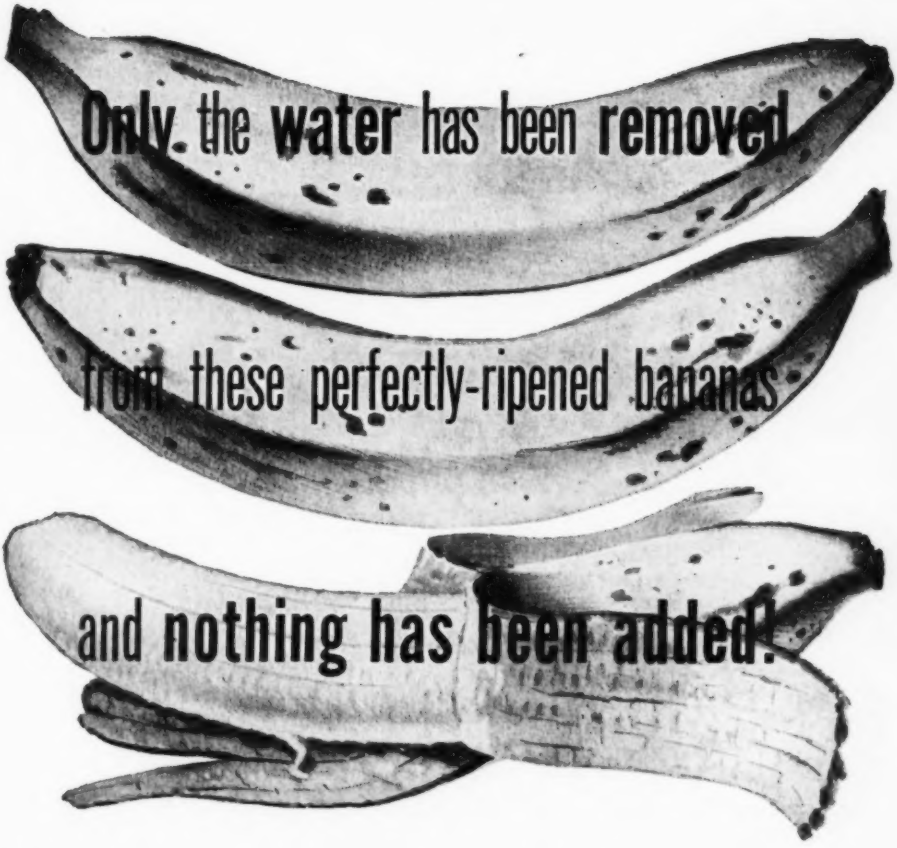

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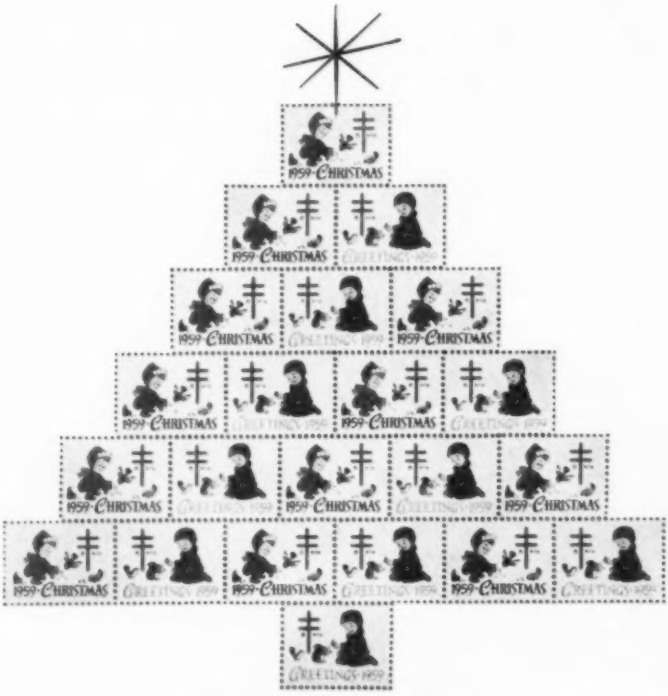

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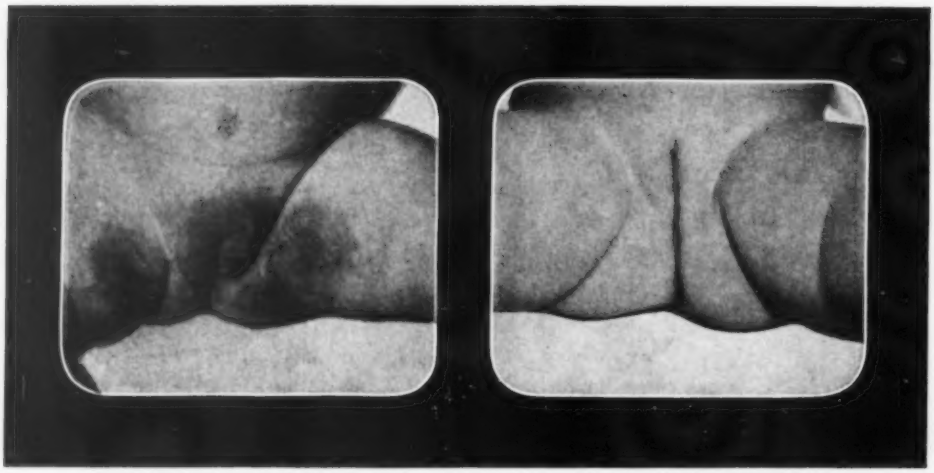

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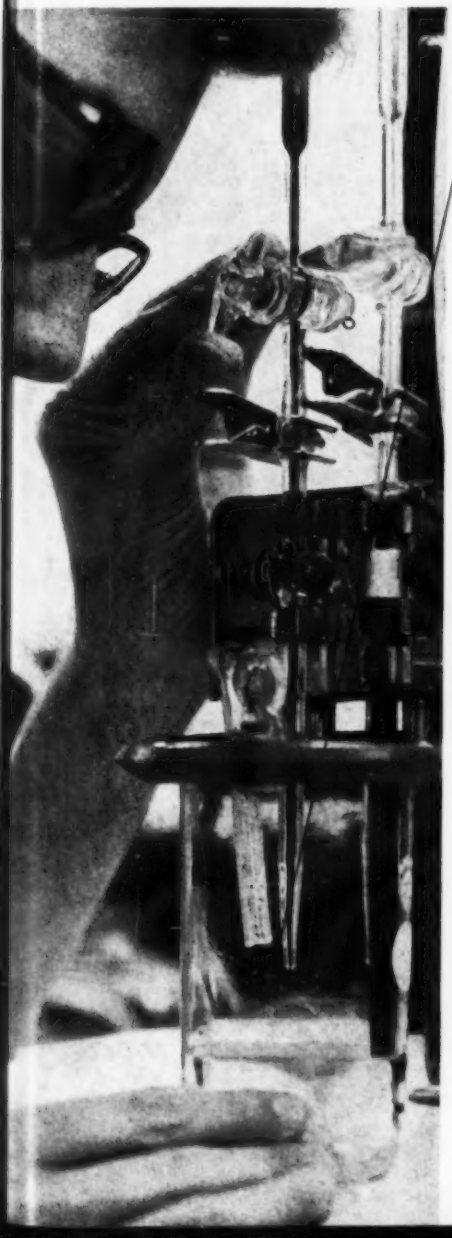

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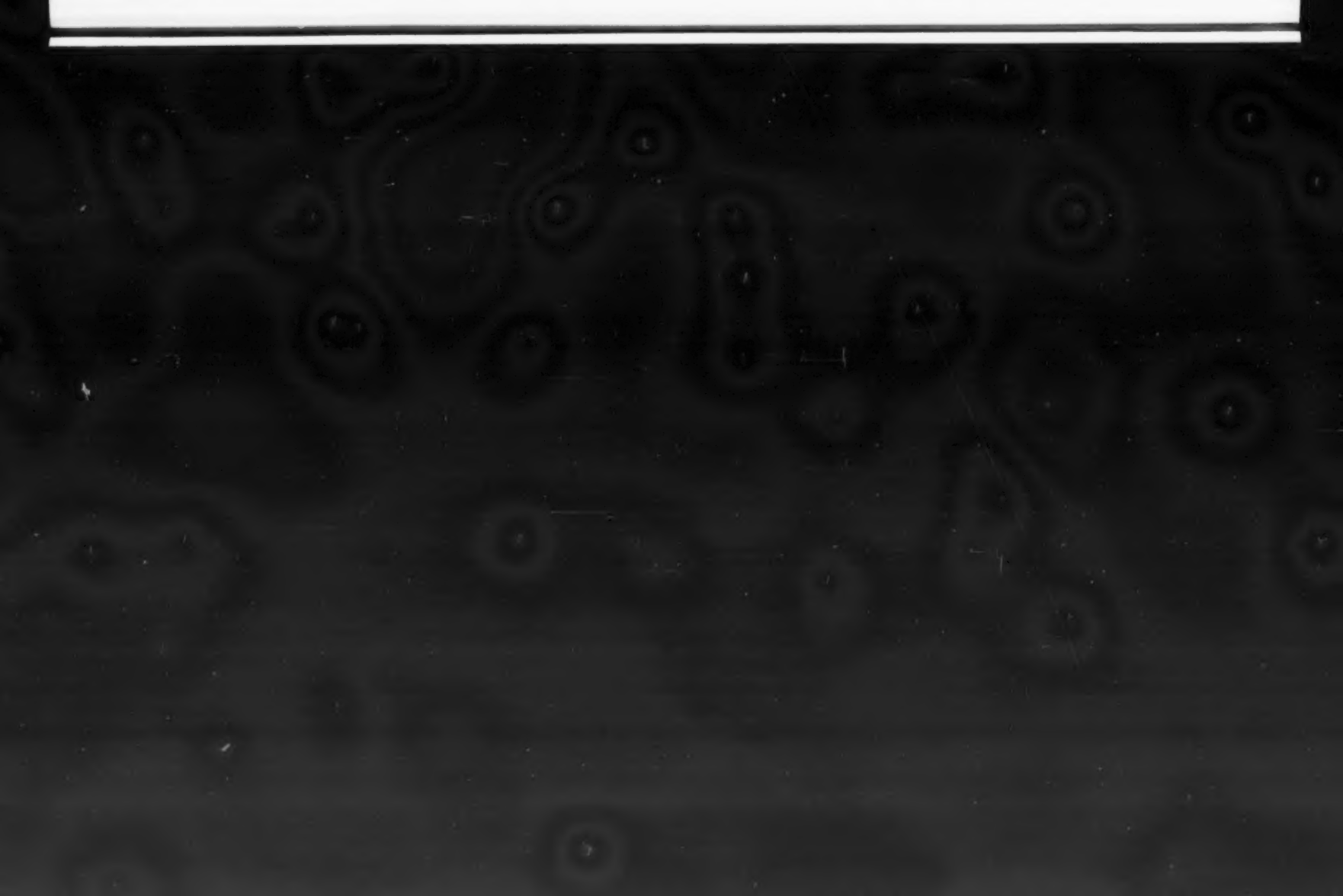

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